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Research report

Dopamine reverses reward insensitivity in apathy following globus pallidus lesions

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ABSTRACT

Apathy is a complex, behavioural disorder associated with reduced spontaneous initiation of actions. Although present in mild forms in some healthy people, it is a pathological state in conditions such as Alzheimer's and Parkinson's disease where it can have profoundly devastating effects. Understanding the mechanisms underlying apathy is therefore of urgent concern but this has proven difficult because widespread brain changes in neurodegenerative diseases make interpretation difficult and there is no good animal model.

Here we present a very rare case with profound apathy following bilateral, focal lesions of the basal ganglia, with globus pallidus regions that connect with orbitofrontal (OFC) and ventromedial prefrontal cortex (VMPFC) particularly affected. Using two measures of oculomotor decision-making we show that apathy in this individual was associated with reward insensitivity. However, reward sensitivity could be established partially with levodopa and more effectively with a dopamine receptor agonist. Concomitantly, there was an improvement in the patient's clinical state, with reduced apathy, greater motivation and increased social interactions. These findings provide a model system to study a key neuropsychiatric disorder. They demonstrate that reward insensitivity associated with basal ganglia dysfunction might be an important component of apathy that can be reversed by dopaminergic modulation.

1. Introduction

Apathy is widespread in mild forms in many people. Recently it has become clear that it can be a severe behavioural condition in disorders such as Alzheimer's and Parkinson's disease (Marin, 1991; Starkstein and Leentjens, 2008). Defined as a state of impassivity associated with a lack of interest, concern or enthusiasm, apathy is dissociable from depression (Marin, 1991). But despite increasing awareness of the condition, we lack a good biological model. This is partly because attempts to understand underlying mechanisms in neurodegenerative diseases are difficult because of widespread brain changes. In addition it is now appreciated that apathy is unlikely to be a unitary construct but is more likely to be a syndrome that might result from dysfunction in several different component decision-making mechanisms (Levy and Dubois, 2006). Here, we investigate the possibility that one component of apathy might be relative insensitivity

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to rewards mediated by dysfunction in frontostriatal systems.

It has long been known that damage to medial frontal cortex can lead to an apathetic state, with patients demonstrating what has been termed 'abulia': reduced initiation of behaviour, lack of interest in their surroundings and loss of spontaneous emotional expression (Starkstein and Leentjens, 2008). A similar condition can also occur after focal lesions of the basal ganglia (Bhatia and Marsden, 1994), with the most severe presentations associated with bilateral damage (Laplane and Dubois, 2001; Schmidt et al., 2008). Such cases are relatively rare, however, and although many aspects of their behaviour have been reported, there has been very little experimental study (but see Schmidt et al., 2008).

Here we report one such individual with profound apathy following focal, bilateral lesions largely involving the globus pallidus (GPi) of the basal ganglia who provides a rare opportunity to understand both the neurobiology and pharmacological modulation of the condition. We used two oculomotor tasks designed to probe reward-based decision-making. In non-human primates, such behaviour has frequently been studied using eye movements, with internal globus pallidus (GPi) neurons demonstrating reward-related activity on such oculomotor tasks (Hong and Hikosaka, 2008; Shin and Sommer, 2010).

Although many brain regions, including parietal and temporal cortex, are activated by reward, a wide range of studies has now demonstrated that the basal ganglia, orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (VMPFC) make a particularly important contribution to value-based decision-making (Haber and Knutson, 2010), with dopamine playing a critical role in modulating behavioural sensitivity to reward (Schultz, 2007). Emerging studies suggest that dopamine also makes a crucial contribution to effort-based decision-making, overcoming the cost of making efforts to obtain desired goals (Niv et al., 2007; Kurniawan et al., 2011).

Lesions of the medial frontal cortex affect how much effort rats are willing to invest for rewards (Walton et al., 2002, 2003; Rudebeck et al., 2006; Schweimer and Hauber, 2005). Rats are also rendered 'anergic' – employing less effortful feeding behaviour – by disruption of dopaminergic transmission in the nucleus accumbens (Font et al., 2008) or the GABA-ergic system in ventral pallidum (Farrar et al., 2008). Moreover, recent functional imaging in healthy humans implicates medial frontal and striatal regions in effort-based decision-making (Croxson et al., 2009). Taken together, these findings are consistent with the view that frontostriatal dysfunction might be a key component of apathy in human diseases (Cummings, 1993; Levy and Dubois, 2006), specifically by rendering patients unwilling to make efforts for rewards. They also point to the possibility that apathy might be amenable to modulation by dopamine, an hypothesis we were able to test in our rare case with bilateral GPi lesions.

2. Materials and methods

2.1. Participants

KD was a 41 year-old-male with ischaemic strokes affecting the internal segment of GPi bilaterally (Fig. 1), with greater involvement on the left. He recovered physically within days of his stroke but demonstrated reduced spontaneous and social activity. A previously exuberant and outgoing type, he became a reticent and reserved individual. He lacked interest in others and reduced spontaneity of action and thought. He remarked that his friends thought he had become boring. He was disinterested in going out to socialize.

He struggled or failed to achieve simple but important life goals such as returning to work. Indeed, he lost his job but then lacked the impetus even to seek unemployment benefit. After moving apartments, he failed to set up his music system because he "couldn't be bothered", despite being an earnest enthusiast previously. He spent most of his day sitting at home, waiting for his flatmates to return and cook food.

Clinically, he was difficult to converse with. Questions were answered with short, closed responses. He did not initiate any lines of discussion, nor ask any questions. Although he was aware of his change in behaviour, he seemed to show little concern about his condition. He scored pathologically (8/12; scores >4 are abnormal) on the initiative and interest subscales of the Apathy Inventory (Robert et al., 2002). Despite demonstrating pronounced apathy, he did not complain of low mood nor seem objectively depressed. He denied biological symptoms of depression and did not score within the depressed range on several established scoring systems: 10 on Montgomery–Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979), 7 on Beck Depression Inventory (Beck et al., 1988) and 2 on Hamilton rating scale for depression (Hamilton, 1960). Verbal and performance IQ were within the normal range.

Physical neurological examination, conducted independently by three consultant neurologists (authors AL, CT and MH) on four different occasions, consistently revealed normal tone, power and co-ordination in the limbs. There was no breakdown of fine finger movements or bradykinesia, even with distraction. Nor was there any evidence of dystonia or involuntary movement, such as chorea. Postural reflexes were intact and there was no abnormality of gait. Deep tendon reflexes and plantar responses were symmetrically normal. Saccadic, smooth pursuit and vergence eye movements were also unremarkable. Clinical single photon emission computed tomography (SPECT) revealed good presynaptic dopamine transporter (DAT) signal in the caudate and putamen, demonstrating integrity of the nigrostriatal dopaminergic pathway, consistent with lack of physical Parkinsonian signs. Because of the unusual nature of his strokes, a CT angiogram was performed but did not demonstrate any anomalous vasculature. Most such cases of bilateral basal ganglia infarction reported previously have no known established cause. The patient denied using 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy"), a substance which has very rarely been reported to be associated with basal ganglia infarction (Hanyu et al., 1995).

Healthy volunteers, [19 male, non-colour blind, mean age = 41 (SD 5.7); 12 right-handed] were recruited by website advertisement and from the UCL Psychology Department's subject pool, with local ethics committee approval. They completed both experimental tasks during a 1 h testing session. On the Barratt Impulsiveness Scale [BIS-11 (Patton et al., 1995)] their mean total score was 65.3 (SD 11.6). Written consent was obtained from all test subjects, according