is of major interest because the MCT1 is thought to be essential for axonal energy supply and integrity (Lee *et al*., 2012).

Although we have to await with interest longitudinal studies of oligodendroglial pathology and function in patients that validate the concept, and studies that demonstrate the specificity of these findings for ALS, the work of Lee *et al.* (2012) and Philips *et al.* (2013) provides several novel insights into the pathogenesis of ALS and raises several new hypotheses:

(1) Oligodendrocytes play a role in the pathogenesis of ALS and their contribution to the disease process might act at an early stage, involving integrity of the myelin sheath; energy supply of the axon; or both.

(2) It is remarkable that findings in the SOD1^{G93A} mice mirror those in human patients with sporadic disease. Since the discovery of TDP-43 neuropathology, many investigators have expressed serious doubts on the importance of findings in this frequently used animal model for ALS. This is understandable, because only 1% of patients with ALS carry SOD mutations, yet >95% of patients with sporadic ALS show TDP-43 neuropathology. Most investigators agree that the TDP-43 neuropathology in SOD gene carriers is scarce, at best. Therefore the study by Philips *et al.* (2013) qualifies any black and white interpretation of the pathogenesis based on pathological features.

(3) The increased turnover of oligodendrocytes and their precursor cells in combination with the reduced expression of MCT1 may suggest a role of altered metabolism in the pathogenesis of ALS, since the development of oligodendrocytes and myelination is influenced by glucose and lactate supply, and by MCT1 expression—major drivers of the metabolic state of the cell (Rinholm *et al.*, 2011).

(4) With regard to urgently needed therapeutic implications, jumping to dogmatic conclusions is certainly not justified. There is currently no evidence that an intervention at the level of oligodendroglia is of any benefit *in vivo*. However, the fact that a lack of oligodendroglial MCT1 expression results in death of motor neurons *in vitro* and axonopathy *in vivo* (Lee *et al.*, 2012), presumably by a lack of lactate supply, calls for attempts to modify the energy supply of the cell. Whether human data that show that high glucose levels or high low-density lipoprotein, triglyceride and cholesterin levels are positively associated with either onset or survival of patients with ALS are related issues (Dupuis *et al.*, 2011), the significance of which remains speculative at this stage, remains pure speculation.

(5) On the other hand, the use in inflammatory demyelinating disorders of the CNS of strategies that promote axonal repair by blocking endogenous inhibition of remyelination—in other words inducing increased proliferation of Ng2a cells to oligodendrocytes—is currently debated (Kremer *et al.*, 2011). The studies of Lee *et al.* (2012) and Philips *et al.* (2013) will further strengthen these concepts.

Taken together, it is evident that these studies support the concept that ALS is not a disorder centred on on ecell; that its pathogenesis is stage-specific; and that metabolic aspects, acting at the cellular level, play a role in the pathogenesis. Time will tell whether these novel insights can be exploited therapeutically.

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Sex, drugs and Parkinson's disease

Dopaminergic therapy to relieve motor manifestations of idiopathic Parkinson's disease may inadvertently cause inappropriate hypersexuality (Vilas *et al.,* 2012). Impulse control disorders that include gambling, eating and hypersexuality seem to occur more commonly with dopamine receptor agonist therapy than L-DOPA and can lead to substantial morbidity with social, psychological

and legal consequences (Vilas *et al.,* 2012). The unregulated nature of direct dopamine receptor activation may provide potential clues to the underlying mechanisms. However, the pathophysiological basis for these behaviours remains unknown. Interestingly, dopaminergic pathways also play a key role in brain networks involved in the reward system, and pathological responses in this system may underlie addiction (Volkow *et al.,* 2012). Similarities between addictive behaviour and drug-induced hypersexuality in Parkinson's disease suggest that they may share common pathological brain mechanisms. Thus investigations of brain regions and networks related to dopaminergic-induced hypersexuality in Parkinson's disease could shed light on these potentially common underlying mechanisms and provide clues for rationale treatment. The study by Politis *et al.* (2013) in this issue of *Brain* takes an important step in this direction.

Impulse control disorders including pathological gambling and eating, compulsive shopping and hypersexuality, as well as the dopamine dysregulation syndrome have been described in the context of dopaminergic therapy for Parkinson's disease (Vilas *et al.,* 2012). Similarly, dopaminergic neurotransmission has been linked to drug abuse (Blum *et al.,* 2012). In fact, the dopamine dysregulation syndrome, with parkinsonian patients craving more and more L-DOPA, shares many clinical features with drug addiction (Katzenschlager, 2011). A pathological reward system may underlie addiction, although the precise role of dopaminergic pathways remains controversial (Berridge, 2007). Recently the theory of incentive salience or incentive sensitization has been proposed as the mechanism by which dopamine acts in reward pathways (Berridge, 2007). Incentive salience means that the 'wanting' of stimulus has higher valence than achieving the reward from the stimulus, and this may be mediated by dopaminergic pathways in the mesolimbic system (Berridge, 2012). Hypersexuality in patients with Parkinson's disease undergoing dopaminergic replacement with L-DOPA or dopaminergic stimulation with receptor agonists represents a good model for studying these mechanisms.

Politis *et al.* (2013) investigated this issue in 12 patients with hypersexuality in association with Parkinson's disease and 12 without hypersexuality. They used blood oxygen level-dependent (BOLD) functional MRI to determine responses to visual stimuli in brain regions with subjects either ON or OFF L-DOPA. The visual stimuli included images of dopaminergic medication, food, money, gambling, sexually suggestive behaviours and neutral cues like nature scenes. They found in patients with hypersexuality that L-DOPA blocks deactivation of multiple brain regions including the isthmus of the cingulate gyrus, parahippocampal gyrus, cuneus, claustrum and the insula. These same regions had decreased activity when patients with hypersexuality were OFF L-DOPA and in control patients with Parkinson's disease without hypersexuality both OFF and ON L-DOPA. Visual sexual cues also activated additional regions in patients with hypersexuality in both the L-DOPA ON and OFF conditions. These included orbitofrontal cortex, anterior cingulate, posterior cingulate and ventral striatum–amongst other regions–not seen in the Parkinson's disease control group and not previously reported in normal subjects exposed to sexual cues. Ratings of sexual desire (the 'wanting') after sexual image exposure correlated with BOLD responses in posterior

cingulate and ventral striatum (L-DOPA OFF) and anterior cingulate and medial orbitofrontal cortex (L-DOPA ON) in the Parkinson's disease with hypersexuality group, whereas the degree to which each participant liked the images did not correlate with responses in any brain region. Taken together, these findings add evidence to the theory that dopamine acts on reward pathways through salience of the stimulus (Berridge, 2007). Furthermore, dopamine may interfere with control of circuits important for reducing desire in patients with Parkinson's disease with hypersexuality. Interestingly, sexual visual cues did not induce a response in ventral striatum in the Parkinson's disease group without hypersexuality, whereas others have demonstrated this in subjects without Parkinson's disease (Kringelbach and Berridge, 2009; Oei *et al.,* 2012). Politis *et al.* (2013) did not include a control group without Parkinson's disease in their study.

There are a couple of potential confounds that could have influenced the findings in this study. The patients with hypersexuality were taking more dopamine agonists than the Parkinson's disease control group. Dopaminergic agonists may have longer lasting brain effects than L-DOPA that could bias the BOLD responses as well as the behavioural results. Dopaminergic agonists also may have regional and pathway specificity that differs from L-DOPA. Furthermore, since dopaminergic agonists are more likely to produce impulse control disorders in patients with Parkinson's disease than L-DOPA, the group differences found could be a brain response to drug treatment rather than a manifestation of the disease (Weintraub *et al.,* 2010). This, however, does not negate the importance of identifying circuits that underlie this behaviour. On a more technical note, increasing concern has developed on the potential effects of movement in BOLD functional MRI studies. The authors did a careful analysis to eliminate those scans with identified body movements by excluding volumes that had >2 mm movement and also checked to ensure that movement metrics did not differ across groups. However, this 2 mm standard may not be sufficient. This has become an increasingly critical issue for resting state BOLD studies but may also affect research involving task-related BOLD responses such as the work of Politis *et al.* (2013), although it is more likely to introduce noise thereby reducing sensitivity for the identification of other BOLD signals (Power *et al.,* 2012).

This study contributes to our understanding of hypersexuality associated with Parkinson's disease and raises further questions in the analysis of impulse control disorders in patients with Parkinson's disease exposed to dopaminergic medications. What makes some patients more susceptible to developing impulse control disorders? Do the differences in Parkinson's disease with and without hypersexuality exist prior to exposure to dopaminergic medications? What premorbid factors or biomarkers predict this proclivity? Reliable biomarkers could identify those patients who should avoid dopamine agonists. Would dopaminergic agonists also block the deactivation of the isthmus of the cingulate gyrus, parahippocampal gyrus, cuneus, claustrum and the insula? The report by Politis *et al.* (2013) is an important step in elucidating the pathophysiology of impulse controls disorders in Parkinson's disease as well as their prevention and treatment.

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