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Functional reorganisation and recovery following cortical lesions: A preliminary study in macaque monkeys

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ABSTRACT

Damage following traumatic brain injury or stroke can often extend beyond the boundaries of the initial insult and can lead to maladaptive cortical reorganisation. On the other hand, beneficial cortical reorganisation leading to recovery of function can also occur. We used resting state FMRI to investigate how cortical networks in the macaque brain change across time in response to lesions to the prefrontal cortex, and how this reorganisation correlated with changes in behavioural performance in cognitive tasks. After prelesion testing and scanning, two monkeys received a lesion to regions surrounding the left principal sulcus followed by periodic testing and scanning. Later, the animals received another lesion to the opposite hemisphere and additional testing and scanning. Following the first lesion, we observed both a behavioural impairment and decrease in functional connectivity, predominantly in frontal-frontal networks. Approximately 8 weeks later, performance and connectivity patterns both improved. Following the second lesion, we observed a further behavioural deficit and decrease in connectivity that showed little recovery. We discuss how different mechanisms including alternate behavioural strategies and reorganisation of specific prefrontal networks may have led to improvements in behaviour. Further work will be needed to confirm these mechanisms.

Cortical damage that accompanies traumatic brain injury or stroke often extends beyond the boundaries of the initial injury. This can lead to maladaptive cortical reorganisation and cognitive impairment (Grefkes and Fink, 2014). On the other hand, beneficial cortical reorganisation following injury can also occur and this can lead to recovery of function. Understanding the nature of cortical reorganisation after injury and how this might be promoted is a challenge for research on developing treatments for patients suffering from brain injury.

Resting state functional magnetic resonance imaging (rsFMRI) provides an indirect method of measuring cortical organisation across the whole brain by correlating BOLD activation patterns between pairs of brain areas. Strong correlation implies, at minimum, a "functional" connection, and often an anatomical connection (Deco et al., 2011). Over the past decade, rsFMRI has been used to examine changes in network organisation in healthy individuals as well as patients who have suffered lesions or who have a variety of disorders such as schizophrenia, Alzheimer's and Parkinson's disease (Fornito et al., 2015; He et al., 2007; Siegel et al., 2016, 2018). However, to fully understand the consequences of cortical reorganisation following damage, it is necessary to measure correlations within cortical networks both pre- and post-injury. It is virtually impossible to obtain pre-injury data from healthy human participants, while in patients, presurgical imaging does not reflect the status of a healthy brain. As such, we employ animal models, where we can collect data both before and after a lesion.

Recent studies have looked at functional connectivity following lesions in non-human primates. O'Reilly et al. (2013) sectioned the corpus callosum (with/without anterior commissure section) in monkeys to explore the relationship between structural connectivity and functional connectivity in neocortical areas. Grayson et al. (2016) used designer receptors exclusively activated by designer drugs (a.k.a. DREADDS) to temporarily inactivate the amygdala and were able to show how acute changes in functional connectivity in amygdala-cortical and cortico-cortical networks followed structural connectivity patterns. However, neither study related these changes to behaviour. By contrast, Meng et al. (2016) made neurotoxic lesions in the hippocampi of infant monkeys and correlated the resulting long-term changes in functional connectivity with performance on memory tests when the animals were 8–10 years old.

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These studies are important in demonstrating the utility of studying functional connectivity following lesions in animals. However, to understand how behavioural recovery occurs after brain injury in patients, we need to correlate changes in functional connectivity with behavioural measures as recovery occurs. In the present study, we used rsFMRI to study how cortico-cortical connectivity in the macaque monkey brain changed in response to discrete lesions of the prefrontal cortex over an extended period of time; and how these changes related to behaviour. Specifically, we examined lesions of the cortex in upper and lower banks of the principal sulcus, which we refer to from here onwards as "PS-lesions".

We chose to focus on PS lesions for several reasons. First, it is well known that lesions there reliably abolish the ability of monkeys to perform delayed response and delayed alternation tasks (Funahashi et al., 1993a; Miller and Cohen, 2001; Passingham and Wise, 2012). Tasks such as these are frequently used to probe working memory, a common impairment suffered by patients with damage to prefrontal cortex.

Second, numerous electrophysiological studies have examined the function of neurons near/within the principal sulcus (e.g., Funahashi et al., 1989; Funahashi et al., 1990, 1991; Funahashi et al., 1993a, 1993b; Kojima and Goldman-Rakic, 1984; Lebedev et al., 2004; Meyer et al., 2011) and our understanding of the characteristics of these neurons and their role in working memory is relatively sophisticated.

Finally, these areas are known to have extensive anatomical connections to other frontal regions as well as with parietal and temporal regions (Petrides and Pandya, 1984; Saleem et al., 2014; Yeterian et al., 2012). In short, the advantage of studying this system is that it is well characterised, both in terms of its connections and in terms of its physiology and function. It is therefore well-suited to our purpose, which is to examine how an injury to a single region within a network affects connectivity across the network, and the subsequent consequences to performance in a well-established behavioural paradigm.

We trained two monkeys on a location-based and object-based delayed match-to-sample task. We collected rsFMRI data and behavioural data at periodic intervals during the prelesion period. The animals then first received a lesion to both banks of the left PS, including areas 46 and 9/46. Following a post-operative recovery period, we resumed periodic testing and scanning sessions. Later, they received a second lesion to the same region in the opposite hemisphere and they were once again tested and scanned at regular intervals.

1. Materials and methods

All animal procedures were conducted in accordance with the United Kingdom Animals (Scientific Procedures) Act (1986) and approved by the University of Oxford local ethical review panel and the UK Home Office Animal Inspectorate. All husbandry and welfare conditions complied with the guidelines of the European Directive (2010/63/EU) for the care and use of laboratory animals. Two adult male monkeys (*Macaca mulatta*, 8–11 kg), purpose-bred in the United Kingdom, were used in this study. The monkeys were pair-housed with varying forms of environmental enrichment, free access to water, and a 12-h light/dark cycle. Veterinary staff performed regular health and welfare assessments, which included formalized behavioural monitoring.

1.1. Overview

We performed a longitudinal assessment of the effect of lesions to both banks of the principal sulcus (PS) on behavioural performance on two cognitive tasks and related it to changes in functional connectivity (Fig. 1A). Once the animals had reached a predefined level of performance on the behavioural tasks (> 70%), we collected resting state functional magnetic resonance imaging (rsFMRI) data under general anaesthesia at two intervals prior to the first lesion (Fig. 1B). Data from two additional scans, earlier in the animals' training, are not included in the present report. Several days prior to each scanning session, the animals were tested on both location- and object-based delayed match-to-sample (DMS) tasks (see below). Following these two cycles of behavioural testing and scanning, each animal received a lesion to both the dorsal and ventral banks of the left principal sulcus (PS), targeting areas 46 and 9/46 (Fig. 2). Following a post-operative recovery period (approximately 4 weeks), we resumed cycles of behavioural testing and scanning (4 cycles approximately once/3–4 weeks). For the next several months, similar cycles of behavioural testing (but without scanning) continued. After 7 months following the first lesion, the animals received a second lesion to both banks of the right PS (Fig. 2). Following a post-operative recovery period (approximately 4 weeks), the animals were once again tested and scanned (4 cycles, approximately once every 3–4 weeks).

1.2. Behavioural tasks

Behavioural testing took place with the monkeys unrestrained inside small transport boxes (approximately 1 m^3) (see Mitchell et al., 2007 for details). One side of the testing box faced a touchscreen to which the monkey had access. In the 'match-to-location' task (Fig. 1A, left), the monkey was required to touch a red cross that appeared in a random location on the touchscreen. The cross then disappeared and a distractor (blue square) appeared in the centre of the screen and the monkey was required to touch this. After a variable delay (2, 4, 8, or 16 s), three stimuli identical to the sample appeared in three different locations. The three locations included the sample location from the current trial, the sample location from a previous trial, and a third random location. The monkey was required to touch the cued location on the current trial to receive a food pellet reward.

In the 'match-to-object' task (Fig. 1A, right), the monkey was required to touch a cue that appeared in the centre of the touchscreen. There was then a variable delay (3, 5, 9, or 17 s; the extra 1 s was added to approximately match the distractor plus delay durations in the match-to-location task). Two stimuli then appeared on the touchscreen on either side of midline (along the horizontal meridian, equidistant from centre). These included the sample stimulus and a distracter stimulus (randomly allocated to either left or right of midline). The monkey was required to touch the stimulus that had been cued to receive a food pellet reward.

The two tasks were not matched for overall difficulty: based on performance data, the location task was more difficult than the object task (Fig. 3). For each testing cycle, there were 1 or 2 test sessions per task (100–120 trials per session), on different days. The second test session was added from the second post-lesion 1 cycle onwards. For cycles with 2 test sessions per task, data from the two were combined as there was no significant difference in performance between the sessions when summed across all tasks, monkeys, and stages of testing (testing session 1 vs. testing session 2: 82 ± 2 vs. 83 ± 2%, $p = 0.11$, paired *t*-test).

Because of the relatively long delays between testing cycles (several weeks), we began each cycle with shorter 'warm-up' sessions (40–100 trials). These were held over two days prior to actual testing sessions in order to re-introduce the animals to the process of testing. Data obtained during warm-up days were excluded from all analyses.

All performance data (percent correct) were first arcsine transformed (to control for ceiling effects) (Studebaker, 1985) before being analysed using two separate three-way repeated-measures ANOVAs (one per lesion) with each testing cycle corresponding to a unit of replication. The three factors were task (match-to-location, match-to-object), monkey (monkey 1, 2), and experimental stage (pre-lesion-1/2, early post-lesion-1/2, late post-lesion-1/2). We examined all main effects, and the interaction between session and task. Post-hoc Tukey's HSD tests were carried out to identify changes in performance associated with experimental stage. Performance values are expressed as