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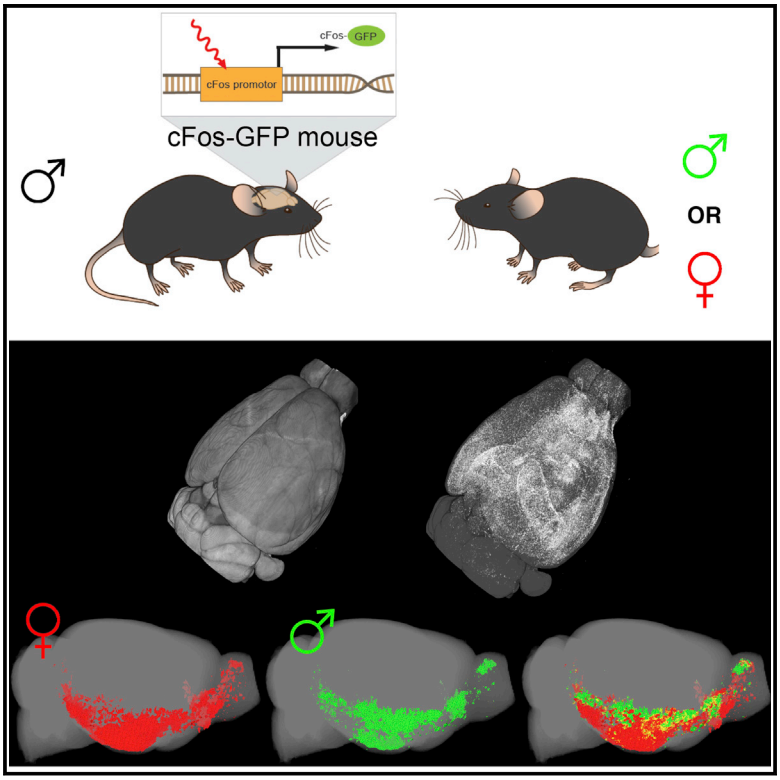
Mapping Social Behavior-Induced Brain Activation at Cellular Resolution in the Mouse

Graphical Abstract



Highlights

- Automated c-*fos* analysis allows mapping of whole-brain activation
- Female and male interactions evoke distinct and shared activation in the male brain
- Activation of specific regions correlates to specific features of social behaviors

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In Brief

Kim et al. use serial two-photon tomography and a pipeline of computational methods to map the induction of the immediate-early gene *c-fos* in response to social behaviors. They provide maps of brain activation evoked during interactions between a male resident and either a male or a female intruder mouse.

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Mapping Social Behavior-Induced Brain Activation at Cellular Resolution in the Mouse

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SUMMARY

Understanding how brain activation mediates behaviors is a central goal of systems neuroscience. Here, we apply an automated method for mapping brain activation in the mouse in order to probe how sex-specific social behaviors are represented in the male brain. Our method uses the immediate-early-gene *c-fos*, a marker of neuronal activation, visualized by serial two-photon tomography: the c-*fos*-GFP+ neurons are computationally detected, their distribution is registered to a reference brain and a brain atlas, and their numbers are analyzed by statistical tests. Our results reveal distinct and shared female and male interaction-evoked patterns of male brain activation representing sex discrimination and social recognition. We also identify brain regions whose degree of activity correlates to specific features of social behaviors and estimate the total numbers and the densities of activated neurons per brain areas. Our study opens the door to automated screening of behavior-evoked brain activation in the mouse.

INTRODUCTION

Central to the understanding of brain functions is insight into the distribution of neuronal activity that drives behavior. Local measurements of brain activity in behaving mice can be made with electrodes and fluorescent calcium indicators (Buzsáki, 2004; Grewe and Helmchen, 2009), but such approaches provide information regarding only a very small fraction of the ~70 million neurons that comprise the mouse brain. The detection of elevated levels of the immediate-early genes (IEGs) linked to recent neuronal activity (Clayton, 2000; Guzowski et al., 2005) is a more spatially comprehensive technique. While it lacks the time resolution of electrophysiological recordings or calcium imaging, it does have the potential of providing a complete view of recent whole-brain activity. Once determined, the whole-brain IEG-based map can be used to generate structure-function hypotheses to be probed by high-resolution recordings as well as optogenetic and chemogenetic methods (Fenno et al., 2011; Lee et al., 2014).

Here, we use a pipeline of computational methods that permits automated unbiased mapping of c-fos induction in mouse brains at single-cell resolution, in a similar way as recently described for mapping the induction of the IEG Arc (Vousden et al., 2014). Specifically, we use serial two-photon (STP) tomography (Ragan et al., 2012) to image the expression of c-*fos*-GFP, a transgenic c-*fos* green fluorescent protein reporter (Reijmers et al., 2007), across the entire mouse brain. The activated c-*fos*-GFP+ cells are computationally detected, their location is mapped at stereotaxic coordinates within a reference brain, and their numbers and densities per anatomical brain areas are determined within the Allen Mouse Brain Atlas. Finally, region of interest (ROI)-based and voxel-based statistical tests are applied to identify brain areas with behaviorally evoked c-*fos*-GFP activation.

To demonstrate the application of the computational pipeline to the mapping of behavior-evoked brain activation, we focus on mouse social behavior and generate activation maps representing sex-specific social behaviors in the male brain. Rodent social behavior is an area of intense research, and c-fos mapping, lesion studies, and other functional approaches have been used to identify brain regions that are activated and contribute to male and female sexual behaviors as well as male-male aggressive behaviors (Anderson, 2012; Biały and Kaczmarek, 1996; Brennan and Zufall, 2006; Coolen et al., 1996; Pfaus and Heeb, 1997; Veening et al., 2005; Yang and Shah, 2014). Much less is known, on the other hand, about the brain areas activated during the initial period of sex discrimination and social recognition before the manifestation of the correct behavioral response.

Here, we explore the question of sex discrimination and social recognition by limiting the male-female and male-male interactions to a brief 90 s period, during which the behavioral repertoire comprises only social exploratory activity, such as anogenital sniffing, close following, and nose-to-nose sniffing, without mating or aggression. A side-by-side comparison of the female and male interaction-evoked whole-brain activation revealed (1) a broad activation of areas downstream of both the main and accessory olfactory bulb (MOB and AOB) in the male-female