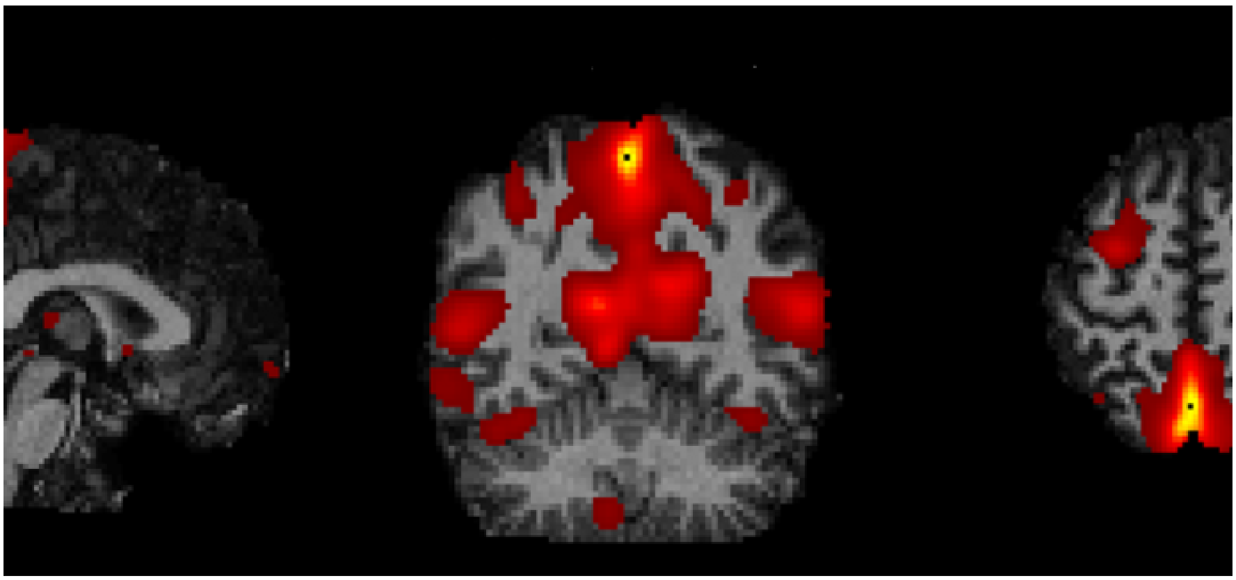
How reliable is resting state fMRI?

January 18 2016, by Emilie Reas



Arguably, no advance has revolutionized neuroscience as much as the invention of functional magnetic resonance imaging (fMRI). Since its appearance in the early 1990's, its popularity has surged; a PubMed search returns nearly 30,000 publications with the term "fMRI" since its first mention in 1993, including 4,404 last year alone. Still today, fMRI stands as one of the best available methods to noninvasively image activity in the living brain with exceptional spatiotemporal resolution. But the quality of any research tool depends foremost on its ability to produce results in a predictable and reasonable way. Despite its widespread use, and general acceptance its efficacy and power, neuroscientists have had to interpret fMRI results with a large dose of partially-blind faith, given our incomplete grasp of its physiological origins and reliability. In a monumental step towards validation of fMRI, in their new *PLOS One* study Ann Choe and colleagues evaluated the reproducibility of resting-state fMRI in weekly scans of the same individual over the course of 3.5 years.

One devoted brain

Although previous studies have reported high reproducibility of fMRI outcomes within individuals, they've compared only few sessions over brief periods of weeks to months. Dr. Choe and her team instead set out to thoroughly characterize resting state brain activity at an unprecedented time scale. To track patterns of the fMRI signal, one dedicated 40 year-old male offered his brain for regular resting-state fMRI sessions. Over the course of 185 weeks, he participated in 158 scans, roughly occurring on the same day of the week and time of day. For comparison – just in case this particular individual's brain was not representative of the general population – a group of 20 other participants (22-61 years old) from a prior study were used as reference.

Reproducibility of brain networks and BOLD fluctuations

The researchers identified 14 unique resting state brain networks. Networks derived from the subject's individual scans were spatially quite similar to those identified from that subject's average network map and the multi-subject average map, and these network similarity measures were highly reproducible. Whereas executive function networks were the most reproducible, visual and sensorimotor networks were least. The relatively low reproducibility of "externally directed" networks could be attributable to the nature of the unrestrained scanning conditions, in which mind-wandering or undirected thoughts could engage an array of sensory experiences. Dr. Choe suspects "that under truly controlled conditions, exteroceptive networks would become more reproducible. Differences in reproducibility in exteroceptive versus interoceptive networks should be seen as an observation that requires follow up study."

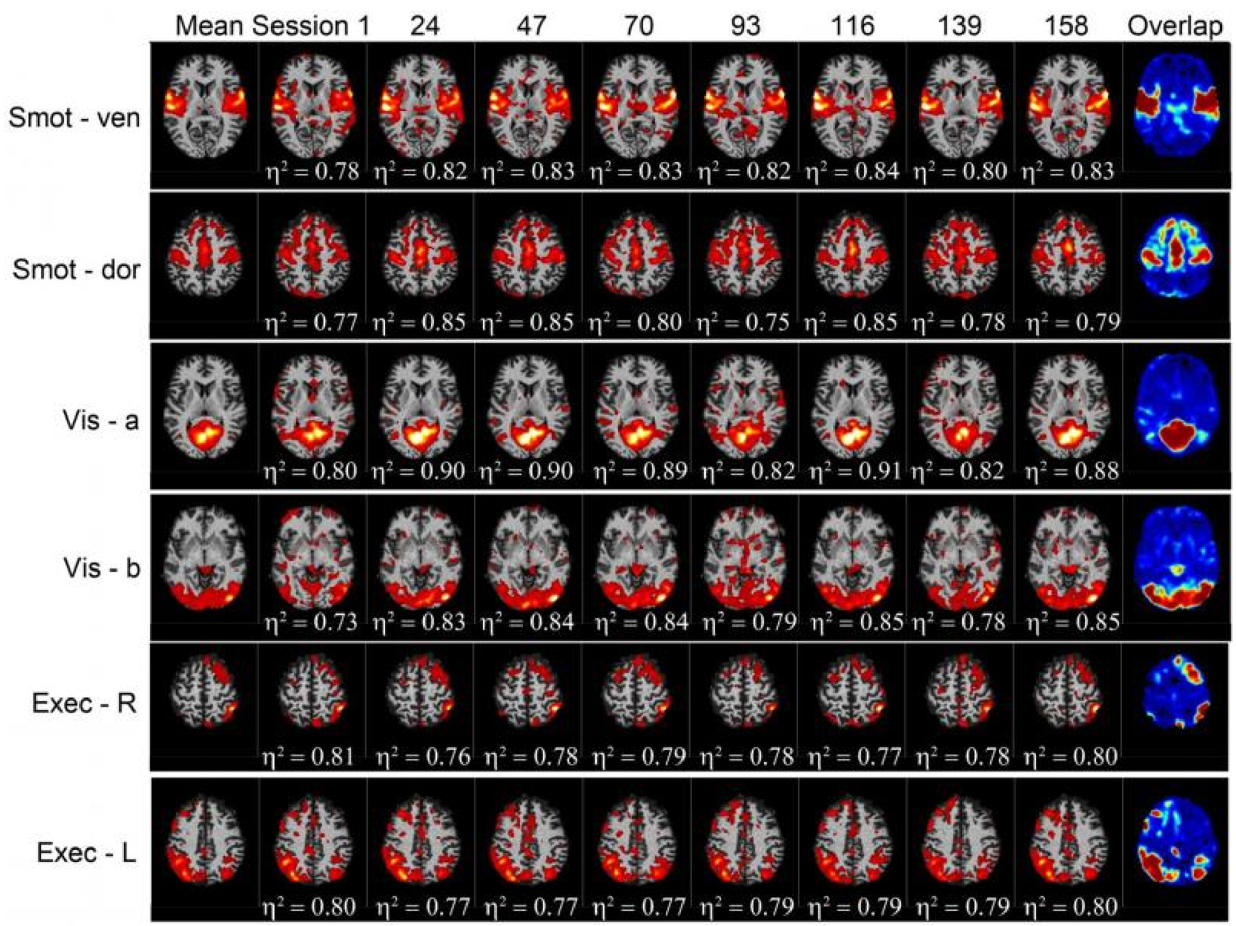


Figure 1. Spatial similarity of weekly fMRI sessions for sensorimotor, visual and executive networks. Credit: Choe et al., 2015

The basic signal underlying fMRI is the blood oxygen level dependent (BOLD) response, a measure of changes in blood flow and oxygenation thought to reflect vascular and metabolic responses to neural activity. The magnitudes of BOLD fluctuations were similar both across the single subject's scans and the group's scans, although these fluctuations were generally more reliable within-subject. Similar to the spatial overlap between networks, BOLD signal in executive networks was most reproducible, while that in default mode and sensorimotor networks were least reproducible across the subject's sessions.

Between-network connectivity

In the brain, no network is an island, but rather, is in constant communication with other regions, near and far. This functional connectivity can be assessed with fMRI by computing correlations in the signal between areas. As might be expected, connectivity was highest between networks involved in related functions, for example between sensorimotor and auditory networks, and between sensorimotor and visual networks. Connectivity between networks was similar in the single subject and multi-subject datasets, and was highly reproducible both across the single subject's sessions and within the multi-subject dataset.

fMRI over the years

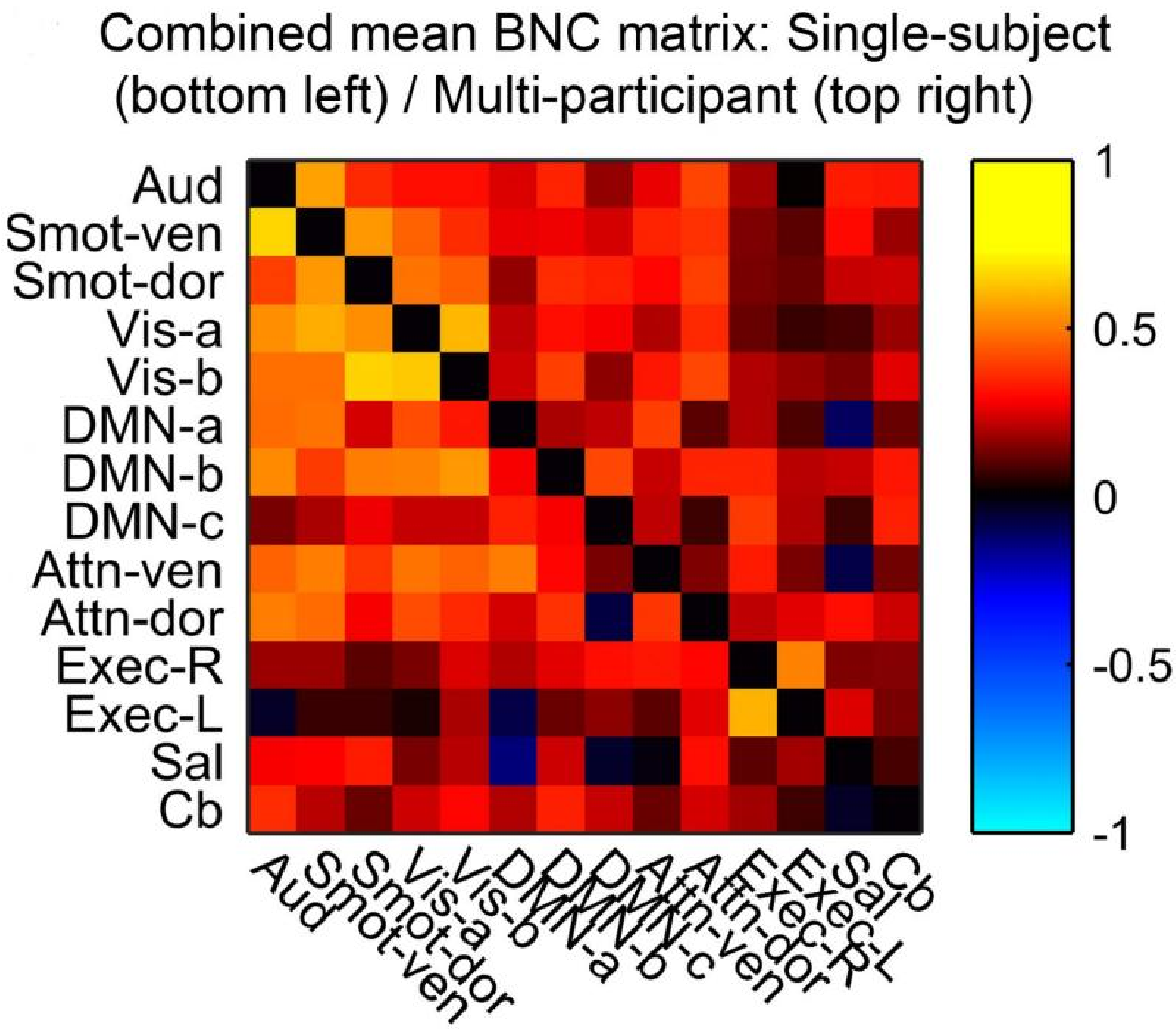


Figure 2. Between network connectivity for single-subject and multi-subject datasets. Credit: Choe et al., 2015

A unique advantage of their study design was the rich temporal information provided from repeated scanning over a multi-year period. This allowed them to not only assess the reproducibility of the BOLD signal, but also to explore trends in how it may change with the passage of years or seasonal fluctuations. Significant temporal trends were found in spatial similarity for the majority (11 of 14) of networks, in BOLD fluctuations for two networks, and in between-network connectivity for many (29 of 105) network pairs. All but one of these trends were positive, indicating increased stability of the fMRI signal over time. What drives these changes over the years isn't entirely clear. It could simply reflect habituation to the scanning environment, for example, if the experience becomes increasingly repetitive and familiar with exposure. Alternatively, the authors suggest, it might involve physiological changes to the aging brain, such as synaptic or neuronal pruning. Over the 3.5-year study, the 40-year old participant indeed showed decline in his gray matter volume; this neural reorganization could feasibly impact the stability of the fMRI signal. However, Dr Choe cautions that "although three years is a long time, it is certainly not long enough to address the issue of say, an aging brain."

Notably, many networks showed annual periodicity in their spatial similarity (9 of 14 networks) and BOLD fluctuations (3 networks). These measures also correlated with the local temperature, linking reliability of the fMRI signal with seasonal patterns. Although speculative, the authors suggest that this may in part relate to circadian or other homeostatic rhythms that regulate brain activity. Dr. Choe and her group "were surprised to discover annual periodicity in rs-fMRI outcome measures. If future studies, in a large number of participants, find significant annual periodicity in rsfMRI outcomes, then it would be prudent to take such temporal structure into consideration, especially when designing studies in chronic conditions, or for extended therapeutic interventions."

Reason to rest easy?

The findings from Dr. Choe and colleagues' ambitious study provides convincing evidence that the resting fMRI signal is reproducible over extensive time periods, giving reason for cognitive neuroscientists everywhere to breathe a small sigh of relief. Perhaps more importantly, it characterizes the nuanced patterns of its spatial and temporal stability, unraveling how it differs across brain networks and might be vulnerable to moderators such as aging or environment. This new understanding of fMRI dynamics will be incredibly useful to researchers aiming to optimize their fMRI study design, and holds particularly important implications for longitudinal studies in which aging or seasonal effects may be of concern. According to Dr. Choe,

"The high reproducibility of rs-fMRI network measures supports the candidacy of such measures as potential biomarkers for long-term therapeutic studies."

One future application her team is currently pursuing is "using rs-fMRI to study brain reorganization in persons with chronic spinal cord injury, having recently reported significantly increased visuo-motor connectivity following recovery. We are interested in whether such measures can be used as biomarkers for prognosis and to help monitor responses to long-term therapy."

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