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Neural overlap between resting state and self-relevant activity in human subcallosal cingulate cortex – Single unit recording in an intracranial study

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A B S T R A C T

High activity of the default mode network (DMN) has been proposed to be central in processing self-relevant events. Thus far, this hypothesis of DMN function has not been tested directly using neurophysiological techniques. To test for the link between frontal midline DMN activity and self-relevant processing we measured neuronal activity (single-neurons' firing rates) in human subcallosal cingulate cortex (SCC) in the course of Deep Brain Stimulation surgery. We find that firing rates in SCC did not change during the presentation of specifically self-relevant stimuli when compared to the preceding pre-stimulus resting state level. In contrast, we observed significant changes in firing rates during other names in SCC. Such rest-self overlap seems to be specific for SCC since increase in firing rates in response to self-relevant stimuli were observed in another region, the subthalamic nucleus, in a group of Parkinson patients receiving deep brain

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stimulation surgery. These results suggest specific relationship between resting state and self-related activity, rest-self overlap, in specifically SCC as core region of the default-mode network.

1. Introduction

Neuroscientist pioneers like T. G. Brown and K. Lashley suggested the brain contains intrinsic activity that is not driven by extrinsic stimuli (Northoff, 2014a, 2014b; Raichle, 2009, 2010). More recently, this has been supported by the discovery of the default-mode network (DMN), a set of mainly cortical midline regions with high metabolic activity during the resting state (Raichle, 2009, 2010; Raichle et al., 2001). While the existence of the DMN has been well established in both human and non-human animals, the functional role of high intrinsic activity and its modulation by stimuli remains elusive (Hutchison et al., 2012; Mantini et al., 2011; Northoff, Qin, Nakao, 2010, 2014a, 2014b; Rilling et al., 2007).

Functional imaging data show regional overlap of high resting state activity in the DMN with the processing of stimuli closely related to one's own self, i.e., high self-specific stimuli, like one's own name, and during self reflection (D'Argembeau et al., 2005; Gusnard, Akbudak, Shulman, Raichle, 2001; Lou et al., 2011; van der Meer, Costafreda, Aleman, David, 2010; Northoff & Bermpohl, 2004; Qin & Northoff, 2011; Whitfield-Gabrieli et al., 2011). These findings provide indirect support for a functional interpretation of resting state DMN activity to “prepare for upcoming, self-relevant events before they happen” (Buckner, Andrews-Hanna, & Schacter, 2008). However, the inherent limitations of functional imaging make it difficult to disentangle the neurophysiological mechanisms underlying the DMN: For instance, we currently remain unable to identify whether the same neurons support the DMN's intrinsic activity and the processing of self-relevant stimuli. Answers to these questions have important implications for our understanding of DMN, intrinsic and stimulus-driven neural activity, and the neural bases of self.

Most recently, deep brain stimulation (DBS) in the subcallosal cingulate (SCC) has been introduced as a potential treatment in major depression (Lozano et al., 2008; Mayberg et al., 2005). This allows us to undertake single unit recording in a region that not only shows high intrinsic activity in the resting state but also has increased activity during rest and self-relevant processing (D'Argembeau et al., 2005; Gusnard et al, 2001; Qin & Northoff, 2011; Whitfield-Gabrieli et al., 2011).

We therefore set out to directly test, i) whether firing rates in response to self-relevant stimuli (own and unknown names) do deviate and change from the preceding levels of pre-stimulus resting state activity in SCC in patients with major depressive disorder (MDD), and (ii) whether this effect is regionally specific for SCC as part of the DMN when distinguished from regions outside the DMN like the subthalamic nucleus (STN). The STN was chosen as a control because it is a common target of DBS surgery for Parkinson's Disease (PD), as well as due to its known anatomical and functional connectivity within both, motor and limbic pathways. The STN's anatomical connectivity to classical limbic structures is of particular interest as emotional and motivational processing is often assumed to be closely related to self related processes despite the latter being conceptually distinct and dissociated from emotional processes per se (Farb et al., 2007; Kühn et al., 2005; Moran, Macrae, Heatherton, Wyland, Kelley, 2006; Northoff et al., 2009).

2. Methods

2.1. Surgery

Electrophysiological microelectrode recording were done in patients undergoing deep brain stimulation of the subcallosal cingulate (SCC) for Major Depressive Disorder (MDD) or of the subthalamic nucleus (STN) for DBS treatment of Parkinson's Disease (PD). Intra-operative recordings of single neuron data were obtained from 13 patients (9 MDD and 4 PD). Approval from the respective ethics review board in Toronto. Deep brain electrode placement was MRI-guided, done under local anaesthetic, and patients were free of sedatives or psychotropic medications during the course of testing.

2.2. Task

The behavioural paradigm applied intra-operatively in thirteen patients in Toronto was a variant of a recently validated task that include the presentation of twenty-four visually presented names in random order, for 2 s per name, interspersed with a 1–2 s inter-stimulus interval[9]. Eight names were the patient's own name (‘own’), eight were a famous name (‘famous’) and eight were a neutral name (‘neutral’). We used two variations of this task, i) the *original* version had different and unique names for each famous and neutral name presented to test for the self-specificity of the own name and ii) the *modified* version had the same name for each of famous and neutral (‘Elvis Presley’ and ‘Michael Wilson’) in order to control for the repetition effect of the own name (Supplementary Tables).

2.3. Single-unit analysis

Single-units were visually identified on an oscilloscope intra-operatively, and once obtained, a baseline period of activity was recorded, prior to task commencement. Firing data were recorded and stored for off-line analysis using Spike2, a commercially available spike sorting and analysis software (CED; Spike 2). Raw data were sampled at 14,286 Hz and band-pass filtered (>500 Hz) to identify action potentials from single neurons by visual inspection combined with template matching and principle component analysis. Audio triggers that signalled the presentation of each stimulus type (own,