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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ABSTRACT

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
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, Akbukad, Shulman, Raichle, 2001; Lou et al., 2013; van der Meer, Costafreda, Aleman, David, 2010; Northoff & Berrmpol, 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 for 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. 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. 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 bandpass 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,
famous, neutral names) were digitized, and firing rates averaged across all presentations of a specific stimulus type. Epochs were set at between 500 msec prior to stimulus presentation to 1500 msec after stimulus presentation, in 100 msec bins. The ITI was defined as an interval 400 msec in length from −700 msec to −300 msec prior to stimulus presentation, to avoid carryover and anticipatory effects. If the mean firing rate during the first 500 msec of stimulus presentation was greater (or smaller) than 2 standard deviations above (or below) the mean firing rate in the ITI, then the neuron was considered to be “modulated” by the presented stimulus.

3. Results

Our task focused on stimuli with high and low-relevance, namely the patient’s own name presented alongside famous and neutral names. This paradigm was applied intraoperatively during DBS surgery that allowed us to record spiking activity of single neurons measured from high impedance electrodes. In total, we examined activity from 15 SCC recording sites and 16 STN recording sites obtained intraoperatively.

To test the spiking activity of neurons we analysed the firing rate of 50 isolated single neurons (28 SCC, 22 STN) during 9 DBS cases for Major Depression and 4 cases of Parkinson’s Disease. Mean firing rates of SCC and STN neurons were 4.71 Hz and 37.3 Hz, respectively, in line with previously reported spontaneous activity in these areas (Davis et al., 2005; Wichmann & Dostrovsky, 2011). We defined a neuron as modulated if its mean firing rate during the first 500 msec of stimulus presentation was greater or less than 2 standard deviations from the mean firing rate in the inter-trial interval (ITI). Of the neurons tested, 15/28 SCC and 7/22 STN were modulated by the presentation of a name stimulus (Supplementary Table). For both brain regions, there was no significant difference between firing rates during ITI and a pre-task baseline period, suggesting that that ITI firing rate is an adequate proxy for the resting state. The mean firing rate during the ITI period and during the processing of self-specific stimuli (‘own’ name) was on average not significantly different across neurons recorded within the SCC (Fig. 1). In STN, however, when averaged across all neurons tested, there

Fig. 1 – Firing rate analyses of SCC and STN neurons. A) Top left: There was no significant difference in firing rate in the first 500 msec of presentation of either self-relevant (S) or non-self relevant (NS) stimuli in the SCC neurons when compared to the rate during the inter-trial interval (−700 msec to −300 msec indicated by the horizontal dashed line). B) Top Right: An example raster plot and peri-stimulus histogram (right panel) from a representative SCC neuron showing lack of response to patient’s own name. X-axis shows time in sec. relative to stimulus onset. Duration of the stimuli were 1.5 sec; Bin width = 100 msec. Horizontal line representing two standard deviations above the mean firing rate in the ITI. b) Similar plots as in a) but for neurons in STN. There was a significant difference in firing rate in STN neurons in response to self-relevant stimuli (S) when compared to baseline (p < .05). Raster plots and peri-stimulus histogram show the STN neuron’s response to the patient’s own name.
was a significant increase in firing rate in the first 500 msec following the presentation of the patient’s own name, when compared to the rate in the ITI (Fig. 1). To explore whether these findings extended to differences between self and non-self-relevant stimuli, we collapsed the responses to ‘famous’ and ‘neutral’ stimuli, into a ‘non-self’ category (NS). In SCC neurons, there was on average no significant difference in firing rates between self and non-self relevant stimuli, whereas in STN neurons, there was (p < .05, Fig. 1).

4. Discussion

Our results show different firing rates in response to self- and non-self-relevant stimuli in specifically SCC as distinguished from STN. Specifically, self-relevant stimuli did not induce any change or deviation in SCC single unit activity when compared to the preceding pre-stimulus resting state level. This pattern was specific for self-relevant stimuli (and distinguished from non-self-relevant ones) as well as for SCC (as distinguished from STN). In sum, our results demonstrate for the first time specific rest-self overlap on the cellular level in SCC as typical region of the DMN.

The meaning and functional relevance of the high intrinsic activity seen in midline cortical structures as core regions of the DMN remains unclear, as does its link to neurophysiological processes. One clue is that highly self-specific stimuli that are externally generated and stem from the environment strongly recruit midline regions like the sub-callosal and pregenual anterior cingulate cortex as typical DMN regions (van der Meer et al., 2010; Northoff et al., 2006, 2010). Interestingly, the same regions demonstrate overlap in neural activity between self and the resting state (D’Argembeau et al., 2005; Gusnard et al., 2001; Qin & Northoff, 2011; Schneider et al., 2008; Whitfield-Gabrieli et al., 2011). The exact neurophysiological mechanism underlying such regional overlap remains unclear. Our study demonstrated that the subject’s own name did not lead to significant changes in single-neuron firing rates in SCC. In contrast, SCC firing rates did increase in response to other names. That suggests specific role of self-relevant information processing in SCC further confirming the observed rest-self overlaps in previous imaging studies (D’Argembeau et al., 2005; Gusnard et al., 2001; Qin & Northoff, 2011; Schneider et al., 2008; Whitfield-Gabrieli et al., 2011).

Critically though, this effect was not observed in the STN, where self-specific stimuli generated significant changes in firing rates after the onset of self-relevant stimuli. This is unexpected when considering that the STN does not show high intrinsic ‘resting state’ activity that is typical of areas of the DMN, such as SCC. Moreover, since we recorded from the STN, a structure known to have motor, reward and other limbic projections, the observed link between intrinsic activity and self-specificity in SCC is unlikely due to affective-motivational factors associated with the self (Farb et al., 2007; Moran et al., 2006; Northoff et al., 2009). If so, one would have expected analogous results in both limbic STN and SCC as both regions are implicated in emotional processing. Since this was not the case our findings suggest a special role of the SCC and its high intrinsic activity in processing self-relevance independent of any emotional-motivational component. Since imaging studies have shown an overlap between reward and self-relevant processing, and the STN is known to be involved in reward pathways, modulation of its firing rate in response to self-relevant stimuli may be driven by purely a reward response.

Our study has several limitations. One limitation is that all of the SCC data was collected from patients with severe depression. Since these patients suffer from abnormalities in both their resting state and self, we cannot exclude disease-specific effects as for instance abnormal ruminations or an abnormally increased self-focus (Alcaro, Panksepp, Witzczak, Hayes, & Northoff, 2010; Grimm et al., 2009; Kühn & Gallinat, 2013; Lemogne, Delaveau, Freton, Guionnet, Fossati, 2012, 2010; Northoff, Wiebking, Feinberg, Panksepp, 2011). The SCC is known to be involved in both the generation of a sad state as well as in affective regulation, more broadly. Whether or not the results observed here relate to disorders where the sense of self is itself disturbed, as in schizophrenia, remains to be seen and investigated. The same limitation may also hold with regard to the STN data as they were obtained in PD patients although, unlike depressed patients, they do not show alterations in their sense of self. Further, it could be possible that the observed lack of firing rate modulation in SCC was related to the small numbers of neurons tested and the low basal firing rates of these neurons. It could also be that on a population level, as opposed to single-unit level, modulation of SCC neurons in response to self-relevant stimuli does exist, and was simply not detected using our methods. Future studies should not only test for externally-generated contents but also internally-generated contents like internal thoughts or stimuli from the body (Vanhaudenhuyse et al., 2011; Wiebking et al., 2014). If our assumption is correct, one would expect high self-specific internal thoughts or personally relevant bodily stimuli to show a similar pattern as observed here. An additional limitation stems from the relatively small number of patients in this study and the number needs to be extended in future studies. Moreover, it would be interesting to test other regions of the DMN and investigate whether they show similar patterns of neural activity modulation as the SCC.

In conclusion, our study demonstrates for the first time neural overlap between resting state and self-relevant activity on the cellular level of firing rates. These results contribute to a better understanding of the neurophysiological mechanisms underlying self-relevant processing, and help shed light on the observed high level of intrinsic activity in cortical midline structures as core nucleus of the DMN.

Author contributions

NL, TN, AML, GN conceived of the study and wrote the first draft. AML and GN provided supervision, and reviewed initial drafts of the manuscript. AML, NL, TN, and NK conducted and analysed the results for Experiment 2. AA helped with experimental design and results interpretation. PG and CH provided clinical support, experimental design and parts of the discussion. TW provided help with results interpretation and the discussion. All authors edited, revised and approved of the final draft.
Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2014.09.008.

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