



# I think therefore I am: Rest-related prefrontal cortex neural activity is involved in generating the sense of self



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## ABSTRACT

The sense of self has always been a major focus in the psychophysical debate. It has been argued that this complex ongoing internal sense cannot be explained by any physical measure and therefore substantiates a mind-body differentiation. Recently, however, neuroimaging studies have associated self-referential spontaneous thought, a core-element of the ongoing sense of self, with synchronous neural activations during rest in the medial prefrontal cortex (PFC), as well as the medial and lateral parietal cortices. By applying deep transcranial magnetic stimulation (TMS) over human PFC before rest, we disrupted activity in this neural circuitry thereby inducing reports of lowered self-awareness and strong feelings of dissociation. This effect was not found with standard or sham TMS, or when stimulation was followed by a task instead of rest. These findings demonstrate for the first time a critical, causal role of intact rest-related PFC activity patterns in enabling integrated, enduring, self-referential mental processing.

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## 1. Introduction

Functionally meaningful rest-related brain activity has been attributed to a neural circuitry unique in its activation patterns, termed the ‘default-mode’ network (DMN), which includes parts of the medial prefrontal cortex (MPFC) as well as medial and lateral parietal cortices (Raichle et al., 2001). This network is often found in neuroimaging studies to be transiently or consistently deactivated during various demanding cognitive tasks, and typically shows increased activity during rest compared to baseline (Buckner & Vincent, 2007). The discovery of consistent rest-related activation in this network has revolutionized the scientific conception of ‘baseline’ neural and psychological activity, which by now has become a field of their own (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle, 2009).

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The mental “resting” condition is phenomenologically experienced as a state of spontaneous thought which includes self-referential mental processes (Gruberger, Ben-Simon, Levkovitz, Zangen, & Hendler, 2011; Schlinger, 2009). Even the mere closing of eyes, relative to open eyes, enhances participants’ internal focus (Lerner, Zhdanov, Papo, & Hendler, 2009). In contrast to the rather novel interest of the scientific community in rest-related neural functioning, this rest-related human tendency to continuously think, whenever the awake mind is liberated from attention-demanding tasks, has long been recognized as a fundamental element of the human awareness of a ‘self’ by writers such as James (1892) and Freud (1963). Contemporary neuroscientists have also argued that this rest-related ongoing thought enables humans to maintain a healthy, constant sense of self (Beer, 2007; Damasio, 1998; Gusnard, 2005). According to this notion, be its content straightforwardly related to the thinker or not, rest related mental activity is a self-related, self-generated, self-sustaining function – an integral part of self-awareness which is a pre-requisite for healthy psychological functioning.

Imaging studies have pointed towards an association between the DMN, with emphasis on rest-related pre-frontal cortex (PFC) activity, and self-referential mental processing (Esposito et al., 2006; Gusnard, Akbudak, Shulman, & Raichle, 2001; Knyazev, 2013; Mason et al., 2007; Qin & Northoff, 2011; Schneider et al., 2008). Furthermore, some indications exist for differential contributions of dorsal and ventral medial PFC to this mental state, with ventral PFC elements associated with its self-related aspects (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Northoff et al., 2006). Across these studies, a theoretical framework exists postulating that default activity in MPFC during rest is critical for the wandering of the mind. Following this idea, if this spontaneous thinking is self-related, then disruptions of MPFC activity during rest would be expected to result in subsequent alterations in the sense of self. Despite the obvious theoretical, scientific and clinical implications of this possibility, the causality of this relation is far from established.

Transcranial magnetic stimulation (TMS) is a noninvasive technique utilized to apply brief magnetic pulses to the brain which induce an electric field in the underlying brain tissue. When the induced field is above a certain threshold, and is directed in an appropriate orientation relative to the brain’s neuronal pathways, localized axonal depolarizations or hyperpolarizations (depending on the stimulation protocol) are produced (Pell, Roth, & Zangen, 2011), thus temporarily modifying neural underlying activity.

Low-frequency repetitive transcranial magnetic stimulation (rTMS) is considered a method well suited for studying the contribution of cortical areas, identified by previous functional imaging experiments, to behavior (Knoch et al., 2006; Kwan et al., 2007; Robertson, Theoret, & Pascual-Leone, 2003). A common practice, referred to as ‘offline’ rTMS, includes the application of low-frequency rTMS for several minutes to subsequently disrupt the normal function of brain regions, thus causing a transient ‘functional lesion’ which has been described as lasting several minutes after rTMS has ended (Eisenegger, Treyer, Fehr, & Knoch, 2008). This approach makes rTMS a unique tool for studying potentially causal brain-behavior relations (Robertson et al., 2003). In this study we used the H-coil, a unique deep TMS (dTMS) coil designed to allow relatively deep brain stimulation (Levkovitz et al., 2009; Roth, Amir, Levkovitz, & Zangen, 2007; Roth, Pell, Chistyakov, et al., 2013; Zangen, Roth, Voller, & Hallett, 2005), to induce a ‘functional lesion’ in deep PFC circuits and investigate whether activity in these networks during rest plays a critical role in self-referential mental processes. The ability of this procedure to reach medial parts of the PFC was demonstrated based on modeling and phantom brain measures (Roth, Pell, & Zangen, 2014; Roth & Zangen, 2014; Roth et al., 2007; Roth, Pell, Chistyakov, et al., 2014). Notably, this comes at the expense of focality, and deep-TMS has been shown to stimulate both superficial and deep brain regions underneath the area of stimulation (Deng, Lisanby, & Peterchev, 2012; Roth & Zangen, 2014; Roth et al., 2007; Roth, Pell, Chistyakov, et al., 2014; Roth, Pell, & Zangen, 2014).

Deep-TMS of the PFC has been studied in different populations (Harvey, Van den Eynde, Zangen, & Berlim, 2013; Isserles et al., 2013; Levkovitz et al., 2009, 2015; Spagnolo et al., 2013) and has been shown to have an effect on cognition (Harel et al., 2011; Isserles et al., 2011; Levkovitz et al., 2009). Specifically, preliminary data obtained in the course of a safety study indicated that PFC stimulation with the H-coil, but not with the conventional, more superficial, figure-8 TMS coil, produced reports of a sense of ‘dissociation’ or ‘detachment’ (Levkovitz et al., 2007). As a sense of dissociation may occur during lessened conscious contemplation of the self (Cahn & Polich, 2006), it is possible that, under certain conditions, deep stimulation over the prefrontal cortex interferes with a circuit that affects self-referential mental processing.

The current study was designed to investigate the causal relationship between PFC rest-related activity and self-referential mental processing, utilizing the H-coil to create a transient ‘functional lesion’ in the medial PFC (MPFC) before rest. Self-referential mental functions were assessed before and after rest or task, which were preceded by either dTMS, standard-(superficial) TMS or sham TMS.

## 2. Materials and methods

### 2.1. Participants

Fifty-five healthy individuals participated in the study (28 women; age range: 21–50 years, average age: 27 years, SD: 5.3 years). Participants were screened for contraindications to TMS including any neurological or psychiatric illness. All participants received a monetary reward equivalent to approximately 40 USD for their participation. The local (Shalvata Mental Health Center) and national ethical review boards approved the study and all participants provided written, informed consent after the procedure had been fully explained.

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