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Review article

# A neuroanatomical account of mental time travelling in schizophrenia: A meta-analysis of functional and structural neuroimaging data

Giorgia Abete Fornara[a], Costanza Papagno[a,d], Manuela Berlingeri[b,c,*]

[a] Psychology Department, University of Milano-Bicocca, Milan, Italy
[b] DISTUM, Department of Humanistic Studies, University of Urbino Carlo Bo, Urbino, Italy
[c] NeuroMI, Milan Centre for Neuroscience, Milan, Italy
[d] CIMeC and CeRiN University of Trento, Rovereto, Italy

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ABSTRACT

*Mental time travel* (MTT) abilities could be particularly compromised in schizophrenic patients due to a deficit of the cognitive processes at the basis of remembering the past and imaging the future: constructive processes, theory of mind and self-awareness. Accordingly, we assumed that the neural circuits typically associated with MTT in healthy people might be partially compromised in chronic schizophrenic patients. To quantitatively and anatomically test our hypothesis, we run two meta-analyses using the Activation Likelihood Estimate method: (i) a neurofunctional meta-analysis on MTT in healthy subjects, (ii) a morphometrical meta-analysis on chronic schizophrenia. The results of the two meta-analyses were overlapped in order to identify the candidate regions involved in MTT deficit in schizophrenia. A significant overlap was found in the vmPFC, in the precuneus, in the hippocampus and in the insular cortex.

We assume that MTT deficits in schizophrenic patients may be the results of a complex dysfunctional interaction between the system underlying the creation of self-representation, the constructive system and the salience attribution network.

## 1. Introduction

### 1.1. Mental time travelling: cognitive and neurofunctional signatures

Personal memories play a key role in building and maintaining our self-awareness. According to Tulving (1985) self-awareness can be fragmented into two components: autonoetic and noetic awareness. The former is the ability to mentally represent our protracted existence across subjective and present time (i.e. the feeling of being a unitary entity notwithstanding the time-related changes), while noetic awareness is related to self-knowledge. Autonoetic consciousness is strongly dependent on episodic long-term memory (eLTM), while noetic awareness depends on semantic memory (sLTM) (Tulving, 1985). In this context, episodic memory is a process related to the reconstruction of specific personal events that occurred to the individual. This reconstruction process can be activated within different time-windows, for example referring to past events (e.g. when I was six y.o. I went to Disneyworld with my family), but it can also play a role in imagining future events (e.g. next summer I'll go to Disneyworld with my family).

Tulving in 1985 introduced the expression "*mental time travel*" (MTT) to indicate the human ability to re-experience personal past episodes and to imagine new future plausible scenarios, with a particular feeling involving the sense of Self, our own emotions and thoughts (Tulving 1985). The ability to recall autobiographical episodes and to imagine new plausible personal experiences for the future share more than one cognitive and neurofunctional aspect (Addis et al., 2009; D'Argembeau et al., 2014; Hassabis and Maguire 2007). According to the authors, MTT, either in the past or in the future, would be supported by the ability to build mental scenarios and to self-project our-selves in a different spatial-temporal context without losing the sense of being our-selves; in turn, these complex processes would rely on working memory, autonoetic consciousness, monitoring processes, episodic memory and relational constructive processes (Hassabis and Maguire 2007; Schacter et al., 2008; Viard et al., 2012).

The partial overlap of cognitive processes between "remembering the past" and "imaging the future" (Schacter et al., 2007) suggests that these two constructive processes may share also part of the underlying neurofunctional networks.

According to the *Constructive Episodic Simulation Hypothesis* (Schacter et al., 2007), shared neurofunctional signatures between remembering the past and imaging the future would reflect the activation of episodic memory information. In particular, during the simulation of

* Corresponding author at: Department of Humanistic studies (DISTUM), University of Urbino Carlo Bo, Via Bramante 17, 61029, Urbino (PU), Italy.
*E-mail address:* manuela.berlingeri@uniurb.it (M. Berlingeri).

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**Table 1**
Characteristics of the studies included in meta-analysis 1: neurofunctional signatures of MTT in healthy people.

| | AUTHORS (YEAR) | DESIGN | SAMPLE SIZE | *p-value* (correction) | SPERIMENTAL TASK |
|---|---|---|---|---|---|
| 1 | Abraham et al. (2008) | Block | 20 | 0.05 (FDR) | Recall of personal and non personal past and future episodes |
| 2 | Addis et al. (2007) | Block | 16 | 0.001 | Construction and elaboration of past and future episodes |
| 3 | Addis et al. (2011) | Block | 15 | 0.05 (FDR) | Recall of specific and generic past and future episodes |
| 4 | Addis and Schacter (2008) | Block | 16 | 0.005 | Construction and elaboration of past and future episodes |
| 5 | Botzung et al. (2008) | Event-related | 10 | 0.001 | Recall of past and future episodes |
| 6 | D'Argembeau et al. (2008) | Block | 12 | 0.001 | Imagination of distant and near future scenarios |
| 7 | Gaesser et al. (2013) | Block | 24 | 0.05 (multiple comparisons) | Imagination of future episodes |
| 8 | Hassabis et al. (2007) | Block | 21 | 0.001 | Recall of autobiographical episodes |
| 9 | Holland et al. (2011) | Event-related | 31 | 0.001/0.05 | Recall of specific and generic autobiographical episodes |
| 10 | Maguire and Frith (2003) | Event-related | 24 | 0.001 | Recall of autobiographical episodes |
| 11 | Oddo et al. (2010) | Block | 15 | 0.05 | Recall of autobiographical episodes |
| 12 | Szpunar et al. (2007) | Event related | 21 | 0.05 | Recall and imagination of personal episodes |
| 13 | Szpunar et al. (2009) | Event-related | 27 | 0.05 (multiple comparisons) | Recall of past and future episodes in familiar contests |
| 14 | Viard et al. (2011) | Block | 12 | 0.001 | Recall of past and future episodes |
| 15 | Viard et al. (2007) | Block | 12 | 0.001 | Recall of autobiographical episodes |
| 16 | Weiler et al. (2010b) | Event-related | 32 | 0.05 (FDR) | Estimate of likelihood of imagined future episodes |
| 17 | Weiler et al. (2010a,) | Event-related | 17 | 0.001 | Recall of past and future episodes |

future events individuals are supposed to recollect personal memories from the past and to build up an imagined future event based on these traces. As a consequence, the core system underlying MTT would be the so-called "constructive system of the brain" that includes the hippocampus (and in particular its anterior portion; Addis and Schacter 2008; Berlingeri et al., 2008), the medial prefrontal associative cortices and the associative parietal regions including the precuneus (Hassabis and Maguire 2009).

With this regard, two recent literature reviews (Schacter et al., 2008; Viard et al., 2012) although controversial, tried to summarize commonalities and differences between the retrieval of autobiographical memories and the imagination of personal future events.

### *1.2. Mental time travelling: psychological and psychopathological considerations*

Remembering the past and imaging the future play an important role in subjective psychological wellbeing: recalling past episodes and imagining possible future scenarios allow people to cope with challenging situations, to improve problem-solving and emotion regulation strategies (Taylor and Schneider 1989).

Moreover, the cognitive functions associated with MTT seem to play a role also in the Theory of Mind (ToM; Premack and Woodruff 1978). For example, Buckner and Carrol (Buckner and Carroll, 2007) suggested that the Self reference, the mental simulation of hypothetic scenarios and the imagination of a spatial context are some of the processes shared by MTT and the ability to predict and comprehend others' feelings and intentions. Likely, the mental construction of alternative scenarios would be the common process underlying those abilities (Hassabis and Maguire 2007). On the basis of these considerations, MTT skills have been studied in several neurological and psychiatric conditions such as amnesia, depression, anxiety and post-traumatic disorders (Williams 1996; de Decker 2001; Raes et al., 2006).

Among neuropsychiatric disorders, schizophrenia has been considered particularly interesting for studying MTT impairments due to several reasons. First of all, schizophrenia is a multidimensional disease whose main symptom is an impaired sense of reality (Gabbard 2005). Secondly, schizophrenic patients typically show a deficit in the sense of self-continuity across time (Danion et al., 2005), something related to Tulving's concept of autonoetic consciousness. Schizophrenic patients are particularly impaired in estimating time-duration of events, and in distinguishing between two sequential stimuli: these difficulties may be linked to the "frozen time feeling" typically reported in phenomenological characterization of these patients (Martin et al., 2014). Moreover, schizophrenic patients suffer a deficit of ToM (Langdon 2005) and, in particular, of the simulation processes that, in turn, rely on hypothetical states (Brüne 2005).

Finally, a number of neuroimaging studies showed that in schizophrenic patients there is a significant decrement of either volume (Nenadic et al., 2012; Shepherd et al., 2012), or metabolism (Tan et al., 2007; Qiu et al., 2010) in key areas for MTT, namely the prefrontal cortex and the medial temporal regions.

This evidence suggests a partial overlap between the MTT network and the areas of grey matter (GM) density loss in schizophrenia. However, so far this hypothesis has never been tested.

### *1.3. Aim of the study*

In the light of the evidence discussed above, it is clinically important to formally assess the overlap between typical schizophrenic-related atrophic patterns and the neurofunctional counterpart of MTT. To this aim, we run two independent meta-analyses using the software GingerALE (Eickhoff et al., 2009; Eickhoff et al., 2012). The first meta-analysis has been designed to identify the neurofunctional correlates, across several independent fMRI studies, underlying autobiographical memory and future imagination in healthy people. Once obtained these neurofunctional maps, we retrieved all the studies that investigated the neuroanatomical reduction of GM density in chronic schizophrenic patients. These data were entered in a second meta-analysis to obtain a map of GM density reductions associated with this disease. We excluded studies which considered either acute patients, or patients with disorders in the schizophrenic spectre (such as, for example, schizoaffetive or schizotypal personality disorder), to control for possible confounding factors (Ellison-Wright et al., 2008).

The results of the two *meta*-analyses were then overlapped in order to identify those brain regions that in healthy subjects are typically associated either with imaging the future, or with retrieving the past, and that are significantly compromised in schizophrenic patients.

## 2. Materials and methods

### *2.1. Studies selection*

#### *2.1.1. Meta-analysis 1: neurofunctional signatures of MTT in healthy people*

Our meta-analysis is based on 17 fMRI studies (see Table 1) published between January 2007 and June 2014, which investigated the neurofunctional correlates of MTT in healthy subjects. Studies were selected by means of the MetaBib system, an academic system capable of consulting at the same time both PsychArticle (http://psycnet.apa.