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Thalamic abnormalities are a cardinal feature of alcohol-related brain dysfunction

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ABSTRACT

Two brain networks are particularly affected by the harmful effect of chronic and excessive alcohol consumption: the circuit of Papez and the frontocerebellar circuit, in both of which the thalamus plays a key role. Shrinkage of the thalamus is more severe in alcoholics with Korsakoff's syndrome (KS) than in those without neurological complication (AL). In accordance with the gradient effect of thalamic abnormalities between AL and KS, the pattern of brain dysfunction in the Papez's circuit results in anterograde amnesia in KS and only mild-to-moderate episodic memory disorders in AL. On the opposite, dysfunction of the frontocerebellar circuit results in a similar pattern of working memory and executive deficits in the AL and KS. Several hypotheses, mutually compatible, can be drawn to explain that the severe thalamic shrinkage observed in KS has different consequences in the neuropsychological profile associated with the two brain networks.

1. Introduction

Alcohol misuse or dependence presents a significant public health problem in most countries. In France, five million people experience medical, psychological, or social difficulties attributable in part to alcohol consumption, and 2 million people are alcohol dependent (Expertise Collective de l'Inserm, 2003). Chronic alcohol consumption results in brain damage and associated neuropsychological deficits, which in turn participate to the maintenance of alcohol dependence. Two brain networks are particularly affected: the circuit of Papez (PC) and the frontocerebellar circuit (FCC), in both of which the thalamus plays a key role. The effect of alcoholism on the thalamus has been known for decades through the prism of the Korsakoff's syndrome (SK; Kopelman, 1995; Korsakoff, 1889). However, more recent neuropathological (Belzunegui et al., 1995; Harding et al., 2000; Kril and Butterworth, 1997) and in vivo neuroimaging (Cardenas et al., 2007; Chanraud et al., 2007; Mechtcheriakov et al., 2007; Pitel et al., 2012; Shear et al., 1992; Sullivan, 2003) investigations revealed shrinkage of the thalamus in alcohol dependent subjects without ostensible neurological complication (alcoholics, AL).

The purpose of the present review is to focus on alcohol-related damage of the thalamus by (1) summarizing the consequences of chronic alcohol consumption on the PC and the FCC (Sections 2 and 3), and (2) comparing the profiles of KS and AL regarding brain damage and cognitive functions associated with the PC and the FCC (Section 4). Such a synthesis of alcohol-related thalamic abnormalities raises new questions, which are discussed in Section 5.

2. The thalamus as a node of the Papez's circuit

2.1. Anatomy of PC and associated cognitive function

The PC involves gray matter nodes of the limbic system such as the hippocampus, thalamus, mammillary bodies and cingulate cortex, interconnected by bundles of white matter fibers. The anterior thalamus receives direct input from the mammillary bodies via the mamillo-thalamic tract and projects to the cingulate gyrus via the internal capsule. The cingulum bundle connects the cingulate

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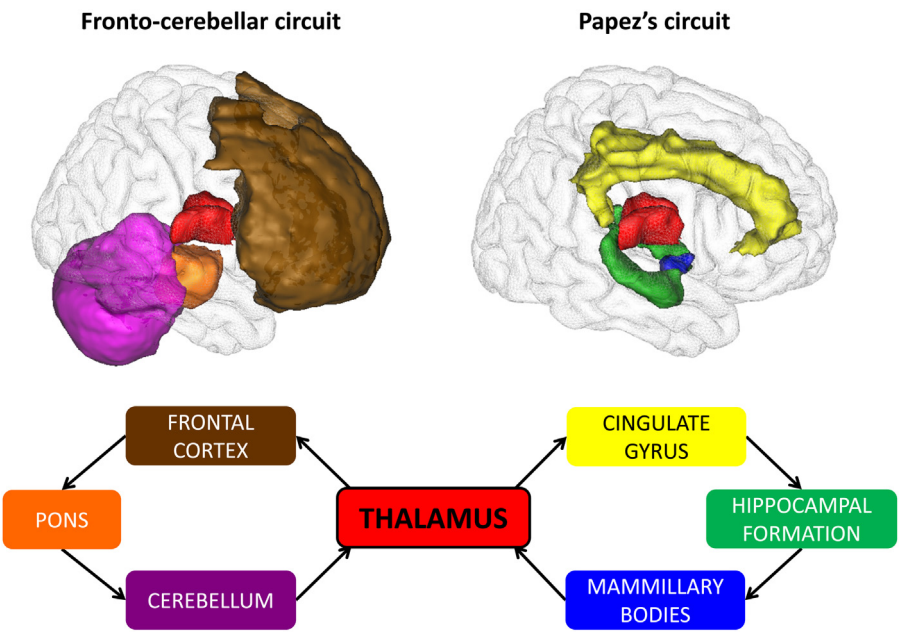

Fig. 1. *The key role of the thalamus (red) in the fronto-cerebellar circuit (FCC) and the Papez's Circuit (PC).* Top left: Regions of the FCC: frontal cortex (brown), pons (orange), cerebellum (purple) with the vermis illustrated in a slightly lighter shade of purple; Top right: Regions of the PC: hippocampal formation (green), mammillary bodies (blue), cingulate gyrus (yellow). Bottom: schematic of the thalamus shared between the FCC and PC. Black arrows indicate the direction of the connection within the two networks. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

gyrus to the entorhinal cortex and hippocampus, which projects to the mammillary bodies through the fornix (Fig. 1).

The PC is mainly involved in mnemonic functions and notably in episodic memory, which is currently described as the memory system in charge of the encoding, storage and retrieval of personally experienced events, associated with a precise spatial and temporal context of encoding. Episodic memory allows the conscious recollection of happenings and events from one's personal past and the mental projection of anticipated events into one's subjective future (Wheeler et al., 1997). Recollection of episodic events includes autonoetic awareness, which is the impression of re-experiencing or reliving the past and mentally traveling back in subjective time (Tulving, 2001). Of the many components of memory, episodic memory is hierarchically the highest memory system, the most sophisticated but also the most sensitive to pathology and toxicity.

2.2. Alcohol-related damage of the Papez's circuit

2.2.1. Structural brain abnormalities

Alcohol-related damage to the PC occurs well before the development of KS. Brain shrinkage has been demonstrated in the anterior hippocampus (Sullivan et al., 1995), mammillary bodies (Sheedy et al., 1999; Sullivan et al., 1999), thalamus (Cardenas et al., 2007; Chanraud et al., 2007; Sullivan et al., 2003) and cingulate cortex (Pitel et al., 2012) of AL. MRI and diffusion tensor imaging (DTI) investigations have revealed compromised integrity of white matter fibers within PC including the fornix, anterior thalamic radiation and cingulum bundle (Harris et al., 2008; Pfefferbaum et al., 2009; Pitel et al., 2012; Schulte et al., 2010; Trivedi et al., 2013).

2.2.2. Episodic memory deficits

Episodic memory, which relies on the PC, has been examined in AL using various tasks. The use of learning tasks revealed evidence of learning over trials in AL but altered abilities to improve the level of performance with practice compared with controls (Beatty et al., 1995; Butters and Cermak, 1980; Everett et al., 1988; Kopera et al., 2012; Schaeffer and Parsons, 1987; Sherer et al., 1992; Sullivan et al., 1997, 1992; Tivis et al., 1995). Learning difficulties have sometimes been attributed to an impoverished generation of spontaneous learning strategies (Butters and Cermak, 1980; Noel et al., 2012; Sullivan et al., 1992), which may also account for the poor performance on free recall tasks (Noel et al., 2012; Weingartner et al., 1996). The spatiotemporal context of encoding is also impaired in AL (Pitel et al., 2007; Sullivan et al., 1997) and AL patients tend not to recall complete episodes, i.e., correct factual information associated with the correct spatiotemporal context of encoding (Pitel et al., 2007). Lastly, alcoholism leads to a deficit of autonoetic consciousness (Pitel et al., 2007), which reflects difficulties to re-experience or relieve the past. In short, all the components of episodic memory are affected in AL.

2.2.3. Brain–function relationships

Even though one would expect a link between the episodic memory disturbance observed in AL and the neuroanatomical abnormalities in regions involved in episodic memory functioning, i.e. mainly in PC, in vivo imaging studies failed to show any correlation between grey matter macrostructural abnormalities and episodic memory impairments in this pathology. Using diffusion tensor imaging, Chanraud et al. (2009b) confirmed the absence of relationship between episodic memory performance and regional volumes. However, the authors found that low verbal episodic memory correlated with altered gray matter microstructure in parahippocampal areas, frontal cortex and left temporal cortex. Thus, microstructural damage may be a predictor of episodic memory disorders in AL. Episodic memory deficits may also be associated with damage of white matter fiber bundles and tracts, including compromised cingulate bundle and fornix (Pfefferbaum et al., 2009; Schulte et al., 2010; Trivedi et al., 2013), leading to an interruption of this functional brain network.

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