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Distortion of time interval reproduction in an epileptic patient with a focal lesion in the right anterior insular/inferior frontal cortices

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ABSTRACT

This case report on an epileptic patient suffering from a focal lesion at the junction of the right anterior insular cortex (AIC) and the adjacent inferior frontal cortex (IFC) provides the first evidence that damage to this brain region impairs temporal performance in a visual time reproduction task in which participants had to reproduce the presentation duration (3, 5 and 7 s) of emotionally-neutral and -negative pictures. Strikingly, as compared to a group of healthy subjects, the AIC/IFC case considerably overestimated reproduction times despite normal variability. The effect was obtained in all duration and emotion conditions. Such a distortion in time reproduction was not observed in four other epileptic patients without insular or inferior frontal damage. Importantly, the absolute extent of temporal over-reproduction increased in proportion to the magnitude of the target durations, which concurs with the scalar property of interval timing, and points to an impairment of time-specific rather than of non temporal (such as motor) mechanisms. Our data suggest that the disability in temporal reproduction of the AIC/IFC case would result from a distorted memory representation of the encoded duration, occurring during the process of storage and/or of recovery from memory and leading to a deviation of the temporal judgment during the reproduction task. These findings support the recent proposal that the anterior insular/inferior frontal cortices would be involved in time interval representation.

1. Introduction

The ability to perceive and estimate the passage of time is essential for the adaptation to an ever-changing environment and allows us to decide how and when to act. Yet, the neural structures that support time perception and estimation are still a matter of debate (Wittmann, 2013). The data obtained using various types of approaches (e.g., lesion, stimulation and functional neuroimaging studies) tend to suggest that the brain regions involved in interval timing differ depending on the task (implicit vs. explicit, motor vs. perceptive, discrete vs. sequential), the duration range (sub- vs. supra-second) or the stimulus modality (Buhusi & Meck, 2005; Coull & Nobre, 2008; Gooch, Wiener, Hamilton, & Coslett, 2011; Grube, Cooper, Chinnery, & Griffiths, 2010; Lee et al., 2007; Lewis & Miall, 2003a, 2003b; Penney, Gibbon, & Meck, 2000; Van Wassenhove, 2009). According to a recent meta-analysis of neuroimaging studies on temporal processing, the supplementary motor area (SMA) and the right inferior frontal cortex (IFC) appear actually as the only structures presenting significant voxels for motor and perceptive tasks with sub- and supra-second durations (Wiener, Turkeltaub, & Coslett, 2010).

Recently, a number of fMRI studies reported the participation of the IFC, usually in association with the anterior insular cortex (AIC), in a diversity of timing tasks (Kosillo & Smith, 2010, for review), involving duration discrimination (Ferrandez et al., 2003; Lewis & Miall, 2003a, 2003b, 2006; Livesey, Wall, & Smith, 2007; Pouthas et al., 2005; Rao, Mayer, & Harrington, 2001), rhythm perception (Schubotz, Friederici, & von Cramon, 2000) or sensori-motor synchronization (Rubia et al., 2000). Notably, using a time reproduction task in the range of several seconds (i.e. 3, 9 or 18 s) with auditory stimuli, Wittmann, Simmons, Aron and Paulus (2010) highlighted that neural activation was greater in the posterior insula during the encoding phase and, further, that it steadily increased to peak at the end of the stimulus, which is

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typical of an accumulation process. By contrast, they observed a greater activation in the AIC/IFC during the reproduction phase. They concluded that the posterior insula would be involved in the coding of the target duration and that the AIC/IFC would participate in keeping a representation of the encoded duration as well as in the duration judgment elaborated during the reproduction phase.

These findings would support a recent model which proposes that the AIC serves as a neural substrate for awareness of the passage of time because of its unique location at the convergence point of all types of emotional, interoceptive as well as exteroceptive, stimuli (Craig, 2009). Craig suggests that, at each instant, primary interoceptive representations in the posterior insula are integrated, along their posterior-to-anterior progression throughout the insula, with activities related to salient environmental conditions (physical and emotional) captured in other parts of the brain, to produce 'global emotional moments' that are associated with awareness of time and of self. According to Craig, the duration of an event is perceived through the accumulation of 'global emotional moments' (a given time interval corresponding to a given series of 'global emotional moments').

Assuming, first, that the information capacity of such global emotional moments is finite (Craig, 2009), then, in the face of emotionally-charged events, (i.e. when the rate of salience accumulation is high), they should more rapidly be filled so that more of them would accumulate than in the face of emotionally-neutral events over a given time period. The model, thus, readily explains the observation that subjects exposed to a highly-arousing negative event generally overestimate the duration of that event (Angrilli, Cherubini, Pavese, & Mantredini, 1997; Droit-Volet, Brunot, & Niedenthal, 2004; Droit-Volet & Meck, 2007; Grommet et al., 2011; Noulhiane, Mella, Samson, Ragot, & Pouthas, 2007; Tipples, 2008). Assuming also that activity in the insula during timing-related tasks reflects the rate of accumulation of 'global emotional moments', then, increased activity in this brain locus should correlate with a subjective impression of time dilatation. This hypothesis is supported by the fact that, during the encoding of a temporal interval in the hundreds of milliseconds range, the hemodynamic response of the mid-insula correlates with the length of the reproduced interval (Bueti & Macaluso, 2011), as well as by two recent fMRI studies showing that the right AIC/IFC region takes part in the alteration of temporal processing by emotional arousal (Dirnberger et al., 2012; Tipples, Brattan, & Johnston, 2013).

Although it is well-documented that lesions in the basal ganglia or the cerebellum have a deleterious effect on aspects of human behaviors that depend upon precise time estimation (Allman & Meck, 2012; Cope, Grube, Singh, Burn, & Griffiths, 2014; Gooch, Wiener, Wencil, & Coslett, 2010; Ivry, 1996), there are few clinical data focusing on the effect of insular or inferior frontal lesions on temporal processing. The ability to analyze fast tone sequences has been shown to be impaired after damage to the right insula (Griffiths et al., 1997) and deficits in auditory temporal processing have been observed following insula infarction (Bamiou et al., 2006). These studies, however, did not use duration estimation tasks. Interestingly, using voxel-based lesion-symptom mapping (VLSM) in subjects with unilateral hemispheric lesions, it has been shown that lesions in the right IFC were associated with a lower performance (i.e. a higher variability) in a duration discrimination task using sub- and supra-second intervals (Gooch et al., 2011). This result further strengthens the notion that the right hemispheric AIC/IFC is preferentially recruited for explicit timing (Coull & Nobre, 2008; Coull, Davranche, Nazarian, & Vidal, 2013; Kosillo & Smith, 2010; Lewis & Miall, 2006; Wiener et al., 2010).

The aim of the present case report was to determine whether a lesion in the right AIC/IFC would alter the judgment of time intervals and, if so, whether the alteration would be modulated by emotion. The temporal judgment of an epileptic patient with a focal lesion at the right junction of the AIC and the adjacent IFC ("AIC/IFC case") was compared to that of a group of healthy controls as well as to that of four additional epileptic patients without insular or inferior frontal damage ("control cases"). Temporal judgment can be studied using various types of tasks (discrimination, verbal estimation, production or reproduction) in different modalities and duration ranges. We decided here to use a time reproduction task in the supra-second range, similar to the one used in a previous study (Wittmann et al., 2010) in which the AIC/IFC was shown to be specifically activated during the reproduction phase. For the purpose of exploring the impact of emotion on temporal judgment, the task was performed in the visual instead of in the auditory modality. Because of their dynamical structure, auditory stimuli are indeed subject to the caveat that they induce a fluctuating emotional state which may evolve with the sound duration. That is why the time reproduction task designed here included, during the encoding phase, highly-arousing negative and emotionally-neutral pictures that participants had to reproduce the presentation duration (3, 5 or 7 s).

Through this experimental protocol, we expected to gain a better insight into the role of the AIC/IFC in time processing. On the one hand, based on previous functional imaging studies (Kosillo & Smith, 2010; Wittmann et al., 2010), we anticipated that a focal lesion in the right AIC/IFC would provoke an alteration of the temporal judgment, which should be reflected by an impairment in its accuracy (reproduction times would either under- or overestimate the target duration) and/or in its precision (reproduction times would be highly variable). On the other hand, we expected that the healthy control group would reproduce the presentation time of highly-arousing negative pictures longer than that of emotionally-neutral ones. Furthermore, supposing that the AIC/IFC is indeed the brain locus where emotional arousal and temporal processing converge and possibly interfere (Craig, 2009; Dirnberger et al., 2012; Tipples et al., 2013), we expected that the impact of emotion on the temporal judgment of the AIC/IFC case would be greatly altered as compared to that of the healthy controls.

2. Material and methods

2.1. Subjects

2.1.1. The AIC/IFC case

The patient was a 24-year-old right-handed man who has drug-resistant symptomatic right insulo-opercular epilepsy related to pilocytic astrocytoma involving the right operculum and the anterior insular cortex (Fig. 1). The time reproduction task was performed by the patient in March 2012 during the Stereoelectroencephalography (SEEG) exploration performed to delineate the epileptic zone (for a detailed description of the SEEG procedure, see Jonas et al., 2012). Neuroimaging data revealed a focal lesion confined to the AIC and IFC (Fig. 1). Anatomo-pathology revealed a pilocytic astrocytoma. After resection, the patient has been completely seizure free with a follow-up of 22 months, confirming the overlap between the lesion and the epileptogenic zone (Table 1). Neuropsychological assessment was conducted in January 2011. The patient gave informed consent to participate in these procedures, monitored by the appropriate institutional ethics committee.

2.1.2. Healthy control group

The performance of the AIC/IFC case in the time reproduction task was compared to that of a group of seven non-epileptic controls, matched on the basis of age (AIC/IFC case: 24 year-old; healthy control group: 25.14 ± 7.08 years), hand dominance (all subjects were right-handed) and educational level (AIC/IFC case: 11 years; healthy control group: 11.14 ± 0.69 years).

2.1.3. Control cases: epileptic patients without AIC or IFC lesion

Four patients, with drug-refractory epilepsy unrelated to a structural lesion or related to a structural lesion located outside of the AIC-IFC region and undergoing