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Degradation of cognitive timing mechanisms in behavioural variant frontotemporal dementia

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ABSTRACT

The current study examined motor timing in frontotemporal dementia (FTD), which manifests as progressive deterioration in social, behavioural and cognitive functions. Twenty-patients fulfilling consensus clinical criteria for behavioural variant FTD (bvFTD), 11 patients fulfilling consensus clinical criteria for semantic-variant primary progressive aphasia (svPPA), four patients fulfilling criteria for nonfluent/agrammatic primary progressive aphasia (naPPA), eight patients fulfilling criteria for Alzheimer's disease (AD), and 31 controls were assessed on both an externally- and self-paced finger-tapping task requiring maintenance of a regular, 1500 ms beat over 50 taps. Grey and white matter correlates of deficits in motor timing were examined using voxel-based morphometry (VBM) and diffusion tensor imaging (DTI). bvFTD patients exhibited significant deficits in aspects of both externally- and self-paced tapping. Increased mean inter-response interval (faster than target tap time) in the self-paced task was associated with reduced grey matter volume in the cerebellum bilaterally, right middle temporal gyrus, and with increased axial diffusivity in the right superior longitudinal fasciculus, regions and tracts which have been suggested to be involved in a subcortical–cortical network of structures underlying timing abilities. This suggests that such structures can be affected in bvFTD, and that impaired motor timing may underlie some characteristics of the bvFTD phenotype.

1. Introduction

Frontotemporal dementia (FTD) represents the second most common cause of early-onset dementia after Alzheimer's disease, and can be phenotypically classified as being either a syndrome of primary progressive aphasia, or as a pervasive dysfunction in normal behaviour and comportment (Warren et al., 2013). Behavioural variant frontotemporal dementia (bvFTD) manifests as progressive corrosion of normal social interaction and cognitive function. The neurobiological basis for the selective degradation of neural circuits mediating the phenotypic expression of bvFTD is poorly understood. Early diagnosis is often impeded by insidious onset and progression, and phenotypic confusion with other dementia diseases or psychiatric illness (Balsis et al., 2005; Glosser et al., 1995; Gregory et al., 1999; Mesulam, 2001, 2007; Snowden et al., 2003). It is estimated that up to 40% of all cases of frontotemporal dementia (FTD) are caused by an underlying genetic mutation (Rohrer et al., 2010). The most predominant responsible genes are the microtubule associated binding protein tau (MAPT, Hutton et al., 1998), which leads to a cascade of hyperphosphorylated tau; mutations in the gene encoding progranulin (PGRN), which causes FTD with ubiquitin and TDP43 inclusions, and the recently-identified expansion of the chromosome 9 open reading frame 72, which is defined by TDP43 proteinopathy (C9ORF72, DeJesus-Hernandez et al., 2011; Majounie et al., 2012). Various neuropsychological measures have been applied to the study of bvFTD in order to identify the earliest presenting deficits and whether any specific neuropsychological measures may be used as markers of disease manifestation and progression. Extensive examination of this population suggests that the earliest and most prominent features of the disease include a degradation of social cognition and behaviour, and deficits in attention, planning, and executive function (Rascovsky et al., 2011; Snowden et al., 2003).

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Precise timing is essential for many human behaviours (Bueti et al., 2008). Important mental functions involving timing include perception and encoding of temporal information, attention shifting, storage and retrieval from long-term memory, and comparison of the temporal memory with other stored templates (Allman et al., 2011; Allman and Meck, 2012; Grondin, 2010). It is also postulated to contribute to theory of mind (Baron-Cohen et al., 2001). Each of these processes are deficient in bvFTD to some extent, and thus it may be possible that such hallmark deficits observed in this heterogeneous syndrome are at least partially mediated by loss of impairments in or changes to a subjective sense of time and the ability meaningfully to perceive and monitor behaviour according to an implicit timing mechanism (Allman and Meck, 2012; Buonomano and Karmarkar, 2002). Timing has been used as a model system of cognitive dysfunction in neurological disease states, with disorders of time and perturbations in timing mechanisms observed in a number of neurological conditions including Parkinson's disease (O'Boyle et al., 1996; Perbal et al., 2005), Huntington's disease (Hinton et al., 2007; Rowe et al., 2010), schizophrenia (Davalos et al., 2005), frontal lesion patients (Picton et al., 2007) and a single case study of a patient with frontotemporal dementia (Wiener and Coslett, 2008).

There are many different aspects of timing, for example perceiving time, predicting time, being oriented in time, as well as different scales which probably involve different mechanisms (for example sub-second and supra-second timing). Much work has been done to elucidate the neuroanatomical bases underlying human timing in both healthy individuals and those with focal and degenerative brain lesions. Recent reviews on various aspects of timing (Coull et al., 2011; Ortuño et al., 2011) highlight the role of the motor and supplementary motor areas as integral components of a larger thalamo-cortico-striatal cognitive timing circuit. Results from studies in Parkinson's disease (PD) (Harrington and Haaland, 1999; O'Boyle et al., 1996) and cerebellar lesion patients (Spencer et al., 2003), as well as in healthy controls (Bueti et al., 2012; Coull et al., 2013; Gilaie-Dotan et al., 2011; Hayashi et al., 2014; Lewis and Miall, 2003) are often interpreted as reflecting the involvement of both the cerebellum and basal ganglia in broader time-keeping operations (Bueti et al., 2008), suggesting a common network of timing-related areas underpinning the use of time both for action and perception.

Coull and colleagues draw attention to the necessity of differentiating between implicit and explicit timing requirements when examining the neurological substrates of these supposedly biologically-separable concepts. The work presented here focuses on supra-second "motor" timing, a measure of explicit (overt) timing requiring participants to estimate a time interval and produce some overt response (often finger tapping). Coull et al.'s recent review presents evidence that for this form of explicit timing the basal ganglia encode a representation of the stimulus, the supplementary motor area (SMA) is engaged by "online" timing (accumulation of stimulus duration, and hence predicting when to make the motor response) and that frontal cortex is also involved, although findings here are less consistent, and may also indicate the contribution of attention and working memory to supra-second timing tasks. The cerebellum is also posited to play a role in representing duration, particularly in short motor timing tasks where demands on attention and memory are relatively lower than for longer times (Coull et al., 2011; Ivry and Spencer, 2004), although the duration at which cortical input might become more important than subcortical is still debated (see e.g. Witt et al., 2008).

An fMRI study of a self-paced finger tapping task highlighted the role of the SMA, basal ganglia, and right-lateralised frontal and parietal cortices (Coull et al., 2013). This functional specificity of neural regions involved in timing maps onto the "pacemaker-accumulator" information processing account of timing (Gibbon et al., 1984). This is also supported by studies of self-paced tapping in patient populations in which the supplementary motor area (SMA), premotor cortex (PMC), dorsolateral prefrontal cortex (DLPFC), and basal ganglia (BG) were thought to subserve this function (Bechtel et al., 2010; Harrington & Haaland, 1999; Rowe et al., 2010), although a recent meta-analysis only found evidence for basal ganglia involvement in sub-second timing tasks (Wiener et al., 2010).

More recently, emerging evidence suggests that white matter tracts interconnecting the cortical areas implicated in cognitive timing may also play a key role in timing functions (Bueti et al., 2012), including motor timing (Schulz et al., 2014; Ullén et al., 2008). It is likely that motor timing is subserved by a network of cortical and sub-cortical structures. Damage to any one of the components of the cognitive timing circuit, including its anatomical connections, could cause dysfunction in motor timing ability.

Many of the aforementioned structures implicated in paced motor timing ability (Coull et al., 2013; Witt et al., 2008) represent a constellation of anatomical regions that are consistently targeted by FTD pathology, suggesting that paced timing tasks may be sensitive to FTD-related dysfunction. One of the earliest sites of pathological involvement in bvFTD is the striatum (Snowden et al., 2003), an area proposed as the 'core timer' within a cortico–thalamo–striatal cognitive timing network (Allman and Meck, 2012). Although the cerebellum is not commonly conceptualised as a centre of pathology in bvFTD, this structure has recently been implicated in the pathogenesis of the FTD-MND gene c9ORF72 (DeJesus-Hernandez et al., 2011; Mahoney et al., 2012; Majounie et al., 2012). Indeed a recent report suggests that in cases with c9ORF72 mutations, of which bvFTD is the most common phenotype, the cerebellum is one of the earliest and most prominent sites of pathological deposition and subsequent degradation (Mahoney et al., 2012).

Although bvFTD is phenotypically, pathologically and genetically highly heterogeneous, imaging studies suggest that the underlying neurodegeneration and spread of pathological deposition follows a somewhat predictable trajectory (Hornberger et al., 2012). Studies using techniques such as diffusion tensor imaging (DTI) suggest that white-matter degradation can be more extensive than grey matter atrophy in the early stages of bvFTD (Agosta et al., 2012), and that tract degradation follows a somewhat predictable atrophic trajectory (Agosta et al., 2012; Zhang et al., 2013). Grey matter structures particularly relevant to the proposed cognitive timing circuitry, including the basal ganglia and cerebellum, are spread within cerebral white matter; however, to the best of our knowledge, no group study has identified an association between cognitive timing ability and integrity of underlying white-matter tracts, in patients with bvFTD.

The current study employs finger-tapping tasks to examine one aspect of cognitive timing, "motor timing": overt reproduction of an interval. Finger-tapping tasks require participants to button-press in time with a paced metronome (externally-paced), or to keep that beat once the metronome has ceased (self-paced), and are often used to assess timing ability. Such tasks have been shown to provide invaluable measures for tracking the manifestation and progression of disease in persons prodromal to and affected by both Huntington's disease (Bechtel et al., 2010; Rowe et al., 2010) and Parkinson's disease (O'Boyle et al., 1996), and have been used to explore the differential effects of focal frontal lesions on timing performance (Picton et al., 2007).

Several statistical models have been proposed to evaluate performance on such tasks. The most widely-accepted approach is that offered by Wing and Kristofferson (1973), which purports that time can be parcelled out at the neural level into clock and motor contributions to timing ability and variability. Studies of patients with neurological damage have provided some evidence