Desynchronization of pathological low-frequency brain activity by the hypnotic drug zolpidem

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SUMMARY

Reports of the beneficial effects of the hypnotic imidazopyridine, zolpidem, described in persistent vegetative state[1, 2] have been replicated recently in brain-injured and cognitively impaired patients[3-7]. Previous single photon emission computed tomography (SPECT) studies have suggested that sub-sedative doses of zolpidem increased regional cerebral perfusion in affected areas[5, 8], implying enhanced neuronal metabolic activity; which has led to speculation that zolpidem 'reawakens' functionally dormant cortex. However, a neuronal mechanism by which this hypnotic drug affords benefits to brain injured patients has yet to be demonstrated.

Here, we report the action of sub-sedative doses of zolpidem on neuronal network oscillatory activity in human brain, measured using pharmaco-magnetoencephalography (pharmaco-MEG). Study participant JP suffered a stroke in 1996, causing major damage to the left hemisphere that impaired aspects of both motor and cognitive function. Pharmaco-MEG analyses revealed robust and persistent pathological theta (4-10Hz) and beta (15-30Hz) oscillations within the lesion penumbra and surrounding cortex. Administration of zolpidem (5mg) reduced the power of pathological theta and beta oscillations in all regions of the lesioned hemisphere. This desynchronizing effect correlated well with zolpidem uptake (occurring approximately 40 minutes after acute administration) and was coincident with marked improvements in cognitive and motor function. Control experiments revealed no effect of placebo, while a structurally unrelated hypnotic, zopiclone, administered at a comparable dose (3.5mg) elicited widespread

increases in cortical oscillatory power in the beta (15-30Hz) band without functional improvement. These results suggest that in JP, specific motor and cognitive impairments are related to increased low-frequency oscillatory neuronal network activity. Zolpidem is unique amongst hypnotic drugs in its ability to desynchronize such pathological low-frequency activity, thereby restoring cognitive function.

The family of ‘z drugs’ which includes zolpidem, zopiclone and zaleplon are non-benzodiazepine sedative/hypnotic agents usually prescribed (10-30mg) for insomnia[9, 10], taking advantage of their fast absorption, short half-life and resultant limited duration of action. However, over recent years there have been an increasing number of reports that have highlighted the paradoxical ability of sub-sedative doses (2-5mg) of zolpidem to improve cognitive and motor ability for patients not only in persistent vegetative state[1], but also in brain injury[5, 7], idiopathic Parkinson’s disease[11], drug-induced Parkinsonism[3], and dementia[4].

Previous single photon emission computed tomography (SPECT) studies have suggested that there is reduced regional blood perfusion in the affected brain area, with respect to the contralateral hemisphere, suggestive of diminished neuronal activity. Following administration of low-dose zolpidem, SPECT studies in a brain injured patient showed increased perfusion, implying recovery of cortical activity[5].

Here we report results from participant JP, who suffered a major stroke 12 years ago. JP presented with fluent conversational speech but had difficulties comprehending specific words (a specific auditory-verbal deficit) with word finding difficulties and semantic paraphasias. Unilateral somatosensory diminution and abnormal gait were also observed. JP evinced marked cognitive and motor improvement in response to zolpidem (5mg), such that a single daily dose provided symptomatic relief beginning at approximately 40 minutes and lasting for up to 8 hours, consistent with previous reports[1, 5]. In addition to symptomatic relief, previous psychometric assessment of JP suggested improvements in IQ as a

consequence of zolpidem administration, although the specific nature of this amelioration was not identified. Similarly, initial SPECT imaging suggested a reduced cerebrovascular perfusion in posterior left temporal lobe, which was improved following zolpidem administration (*Fig.* 1a & b). These initial observations formed the starting-point for the studies on JP described below, the ultimate purpose of which was to determine the changes in brain activity underlying JP's neurological deficits and, more importantly, to measure how network activity was modulated by zolpidem in relation to recovery of sensorimotor and cognitive function.

We used a multimodal imaging approach, comprising magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (^{1}H MRS) to obtain structural and chemical information from stroke-affected and unaffected brain regions (*Fig.* 1c-g). Spatial information from these scans was used to guide subsequent magnetoencephalography (MEG) investigation through placement of 'virtual electrodes' in anatomically defined loci to determine the profile of focal electrical activity across the cortex prior to, and following drug administration.

Initial observations from ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO) SPECT of reduced left temporal lobe perfusion (*Fig.* 1a), which were improved by zolpidem administration (*Fig.* 1b), were contextualized by the visualization of the left lateralized lesion using MRI (*Fig* 1c). A generalized partially parallel acquisition (GRAPPA) image of a T2-weighted scan of JP in the sagittal plane (*Fig.* 1d) revealed the extent of the left temporal lobe lesion, impinging on language and motor areas. Grey and white matter visualization was used to identify regions for

further analysis within the lesion, the intact contralateral hemisphere and the lesion penumbra (denoted A, B and C respectively). Subsequently, using co-registration with the anatomical MRI[12], these loci were investigated using MRS and MEG. MRS analysis of the lesion site revealed an absence of typical metabolic markers associated with viable brain tissue, such as N-acetyl-aspartate (NAA), creatine (Cr), choline (Ch) and *myo*-inositol (mI), although a lactate (Lac) peak, commonly seen in cerebrospinal fluid (CSF) could be seen (*Fig.* 1e). Investigation of the contralateral hemisphere revealed a typical chemical spectral profile, with normal ratios of NAA, Cr, Cho and mI (*Fig.* 1f). However, whilst the lesion penumbra location also showed relatively normal ratios of these metabolites, the spectrum was dominated by an abnormally high Lac peak (*Fig.* 1g), suggesting a degree of ongoing metabolic stress within neuronal populations close to the original lesion.

MEG virtual electrode analysis, derived from the Synthetic Aperture Magnetometry (SAM) beamforming method[13], was used to derive power-spectra from the voxels used in MRS analysis (1-60Hz). A MEG signal was not detectable in the lesion voxel (*Fig.* 1h), whereas the contralateral voxel was typified by a normal amplitude spectrum with moderate power across the low-frequency range (*Fig.* 1i). Analysis of the penumbral voxel revealed strikingly high power in the theta frequency range (peak 8Hz) superimposed on a high degree of broadband low-frequency oscillatory activity (*Fig.* 1j). This pattern of slow wave activity, seen first in the lesion penumbra, was evident across all virtual electrode placements ipsilateral to the lesion, including the dorsolateral prefrontal cortex (DLPFC), parietal lobe, superior temporal lobe and sensorimotor cortex (SMC), and was not evident in

contralateral electrodes. Furthermore, in the ipsilateral sensorimotor regions adjacent to the lesion an elevated beta frequency oscillation (peak 25Hz) was also evident (*Fig.* 2c & k).

Figure 1 Here

Double blind, placebo controlled pharmaco-MEG analyses of a 60 minute period following drug administration, used SAM techniques[13, 14] to identify the spatial distribution of power change in delta (1-3Hz), theta (4-10Hz), alpha (7-14Hz), beta (15-30Hz) and gamma (30-80Hz) frequency bands. This approach revealed a powerful desynchronizing effect of zolpidem on the enhanced theta and beta activity seen within ipsilateral cortex, in both language-associated (*Fig*.2a & e; *Fig.* 3b) and sensorimotor areas (*Fig*. 2c & f; *Fig* 3a). By contrast, we observed no effects of zolpidem on baseline low-frequency activity in electrodes placed contralateral to the lesion (*Fig*.2b & d). When we repeated these experiments using a placebo we observed no effects on MEG activity. Conversely, following zopiclone administration at sub-sedative dose (3.5 mg), we noted a striking, bilateral, broadband increase (*Fig*. 2g-l) in oscillatory activity in the beta frequency range (15-30 Hz), consistent with previous MEG observations using a similarly non-specific $GABA_A$ receptor modulator[15]. These data indicate that 12 years following initial insult, neuronal tissue surrounding the original lesion continues to exhibit pathological behavior in the form of slow wave oscillations and also that zolpidem has a unique, desynchronizing effect that is specific to such activity.

Figure 2 Here

We next addressed the question of how focal desynchronization was related to cognitive and sensorimotor function in JP through MEG measures of language and motor function. The use of independent isometric contraction of the left and right hands afforded localization of respective contralateral SMC through peak beta frequency desynchronization (*Fig.* 3i) consistent with previous observations[16]. Similarly, category naming and covert letter fluency tasks were employed to localize language related areas through peak desynchronization (*Fig.* 3j & k), consistent with previous observations in the DLPFC[17]. These latter activations were key, since these tasks typify the language difficulty that JP exhibited under drug-free conditions. We found a strong spatial and frequency domain correspondence between the zolpidem-induced (*Fig.* 3a & b) and functional desynchronization events (*Fig.* 3i-k), suggesting that zolpidem administration had direct functional consequences within modalities in which JP is compromised.

With the aim of identifying the temporal profile of oscillatory changes that underlie the improvements in cognitive and sensorimotor performance, we implemented a virtual electrode reconstruction of discrete neuronal activity at the peaks of desynchronization in both the passively and functionally identified loci. This method is a measure of discrete neuronal activity[18] resembling those made at the local field potential level[19]. We reconstructed the envelope of oscillatory power over the entire 60 minute duration following drug administration. This approach

revealed that the abnormally high sensorimotor beta oscillations observed prior to drug uptake were persistent, and were chronically suppressed following zolpidem administration (*Fig.* 3c & f). Similarly, abnormally high and persistent theta oscillations observed in language performance areas such as DLPFC were also suppressed by zolpidem (*Fig.* 3d, e, g & h).

Figure 3 Here

The onset of these reductions in synchronous power occurred at 35-45 minutes post drug administration, consistent with both JP's self-reported improvements on language-related tasks and the pharmacokinetic profile of zolpidem. Neither the therapeutic benefit nor the associated desynchronization was observed following administration of zopiclone or placebo. Psychometric evaluation of JP used the WAIS-III[22] to evaluate drug-enhanced cognitive performance, firstly with zolpidem and then 6 months later without zolpidem. Test-retest gains in performance across WAIS-III Index and IQ scores due to practice effects are well documented[20]. Therefore, the order of administration was chosen to underestimate rather than overestimate gains due to zolpidem. JP achieved highest scores on the Perceptual Organization Index, with scores falling in the top 12-18% of his age group. In the absence of zolpidem results revealed deterioration in performance across all Index and IQ scores with the exception of the Working Memory Index, which remained within the bottom 1% of the population across both test occasions. The greatest change was evident in the Verbal Comprehension Index and JP's

standardized score dropped by 27 percentile points, moving from the ‘average’ to the ‘low average’ range (*Fig.* 4); these observations were consistent with clinical presentation.

Figure 4 Here

In summary, in JP, a left temporal lesion resulted in an increase in pathological theta and beta frequency oscillatory power compared to the undamaged contralateral hemisphere. In sub-sedative doses, zolpidem was capable of suppressing pathological slow wave activity to a level that allowed functionality to return. It seems reasonable to infer that the action of zolpidem in brain injury is related to its unique dose-dependent selectivity for $GABA_A$ receptors containing the α-1 subunit. The desynchronizing effect of zolpidem may reflect the differential distribution of α-1 subunit containing $GABA_A$ receptors between specific interneuronal subtypes sub-serving oscillatory activity[21]. Consistent with this interpretation, non-selective $GABA_A$ receptor modulators such as lorazepam[15] and zopiclone do not desynchronize neuronal network activity, indeed, oscillatory power is enhanced.

Synchronization across extensive neuronal populations can result in a marked reduction in information transfer. Specifically, a broad elevation in the mutual information between cortical regions will reduce the capacity for computational processing. In this scenario, the consequent reduction in the complexity of information encoding would provide an explanation for the cognitive

decline observed under pathological conditions. Exaggerated slow wave activity is a feature common to a diverse array of neuropathologies, including traumatic brain injury[22], stroke[23], Alzheimer's disease[24], and schizophrenia[25] and therefore may represent a biomarker for impaired CNS functionality. Desynchronization of pathological oscillatory activity appears to improve CNS function. For example, in Parkinson's disease, dopamine replacement therapy has been demonstrated to reverse augmented beta activity, which correlates with symptomatic relief[11, 26]. Similarly, administration of dopamine agonists is efficacious in the treatment of brain injury[27]. Furthermore, following deep brain stimulation positive functional outcomes linked to a desynchronization of EEG oscillatory activity have been observed in persistent vegetative state[28].

It is widely accepted that event-related desynchronization (ERD) is a central phenomenon in normal brain activity[29] and ERD has been established as a feature of sensorimotor[16] and cognitive processing[17]. In JP, the high power and persistent nature of pathological oscillations appears to represent an obstacle to adequate ERD; this inability to desynchronize may represent a barrier to effective computation in neuronal networks. Here we show that drug induced suppression of this functional barrier affords a return of cognitive performance, typically associated with ERD. As previous evidence suggests, MEG is an optimal tool for the identification of slow wave activity[22] as a biomarker of brain dysfunction. In addition, we would suggest that pharmaco-MEG represents a powerful method for the identification and development of future therapeutic interventions.

In conclusion, given the involvement of pathological slow wave oscillatory activity in a wide range of neurological disorders, and the desynchronizing properties of zolpidem as measured using pharmaco-MEG, it seems reasonable to suggest that zolpidem treatment might prove to have a broad therapeutic remit.

Methods Summary

Our participant, JP, presented with sensorimotor and language deficits following major stroke, which were reported to improve following single daily administration of zolpidem. SPECT analysis was used to determine regional perfusion with and without zolpidem. We used structural MRI scans to determine the spatial extent of the lesion and to obtain detailed anatomical information for functional co-registration. Voxels were identified with the left temporal lesion, the lesion penumbra and comparative location contralateral to the lesion. These three voxels were examined using MRS and MEG to identify the chemical composition and power spectra respectively.

JP was tested using a double blind drug study over three days to examine the effects, over a 60 minute period, of zolpidem (5mg), zopiclone (3.5mg) and placebo on intrinsic oscillatory activity across the cortex. MEG data were co-registered with JP's anatomical MRI[12] and analysis was performed using a SAM beamforming method[13, 14] to identify peaks of synchronous power change in response to each of the drugs administered. Additionally, a number of functional tasks were used to localize sensorimotor and language related areas[16, 17].

At the peaks of oscillatory power change, identified from SAM analysis, virtual electrodes were implemented in order to identify the power spectra at the loci pre and post drug. Furthermore, the electrical signals from these loci were band-pass filtered to the peak frequencies in the theta and beta ranges and the envelope of the oscillatory power[30] reconstructed for the 60 minute duration following drug administration. In order to establish the exact nature of JP's cognitive impairments and improvements following zolpidem, a comprehensive psychometric evaluation was performed using the WAIS-III. These were undertaken firstly with zolpidem and then 6 months later without zolpidem, to account for potential practice effects.

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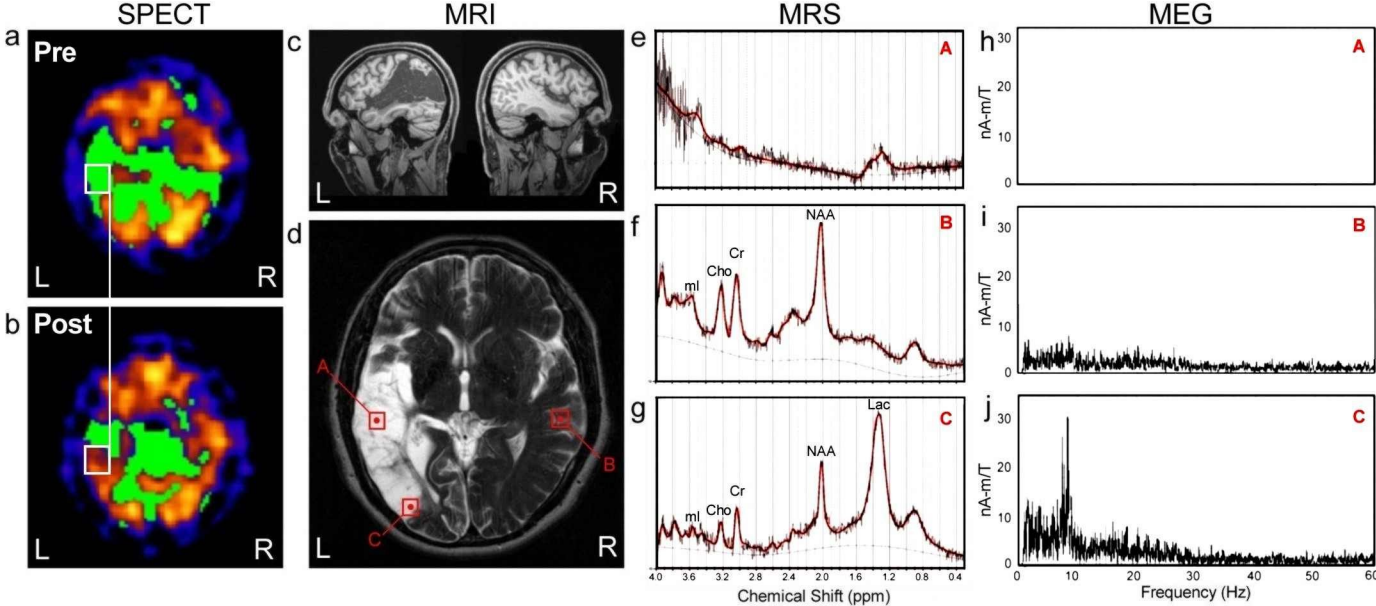
Figure Legends

Figure 1 | Characterization of pathology. SPECT analysis showing cerebral blood perfusion **(a)** before and **(b)** after zolpidem; white boxes indicate left temporal region where perfusion is increased. MRI images showing the extent of the lesion in the left hemisphere in **(c)** a T1 weighted sagittal section and **(d)** T2 weighted axial section; red boxes (A, B & C) indicate lesion, contralateral control and lesion penumbra voxels used for subsequent MRS and MEG analyses. MRS analysis of voxels identified from MRI (**e, f** & **g** derived from A, B & C respectively); abbreviated annotations indicate chemical markers observed. MEG analysis of voxels A, B & C (**h, i** & **j** respectively), showing power spectral analyses (0-60Hz).

Figure 2| Drug induced oscillatory modulation. Results of SAM analyses indicating the spatial distribution of oscillatory power change as a consequence of zolpidem **(a** & **b)** and zopiclone **(k** & **l)** administration; blue indicates a reduction and orange an increase in oscillatory power. **a**, theta desynchronization and **b**, beta desynchronization following zolpidem administration. Power spectral change in left and right DLPFC **(c** & **d)** and left and right SMC **(e** & **f)** pre and post zolpidem administration. Beta synchronization bilaterally in frontal cortex **(k)** and SMC **(l)**, pre and post zopiclone administration. Power spectral change bilaterally in DLPFC **(g** & **h)** and SMC **(I** & **j),** pre and post zopiclone administration.

Figure 3 | Pharmacodynamic profile of zolpidem induced desynchronization. SAM and images co-registered with the 3-dimensional MRI and band-pass filtered virtual electrode traces recorded for 60 minutes post zolpidem administration. Distribution and time-course of desynchronization in the beta **(a** & **c)** and theta **(b, d** & **e)** frequencies. Event-related desynchronization (ERD) in the beta range in response to contraction of the right hand **(i)** and in the theta range in response to category naming **(j)** and covert letter fluency tasks. Virtual Electrode analysis indicates the electrical activity at these peak ERD loci over the 60 minutes duration, band-pass filtered to beta **(f)** and theta **(g** & **h)**. Red lines denote onset of zolpidem-induced cognitive and motor improvements.

Figure 4 | Psychometric analysis of zolpidem mediated improvement. Bar chart reflecting the results of JP's WAIS-III assessments carried out with zolpidem (blue) and without zolpidem (red). Scores are age-standardized and displayed as percentiles.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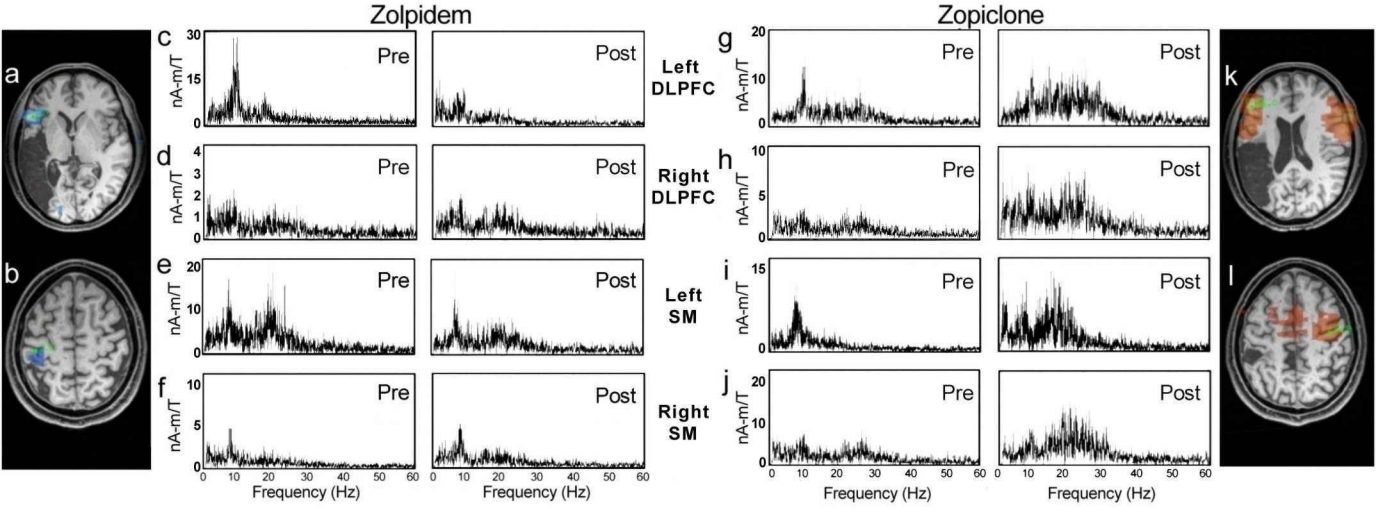
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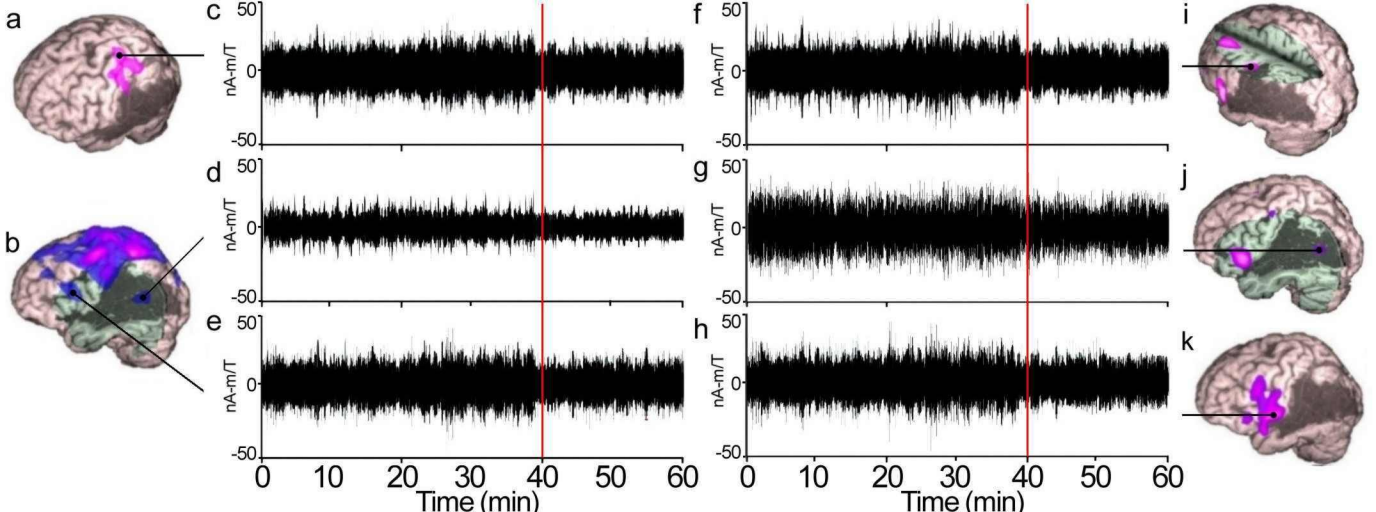
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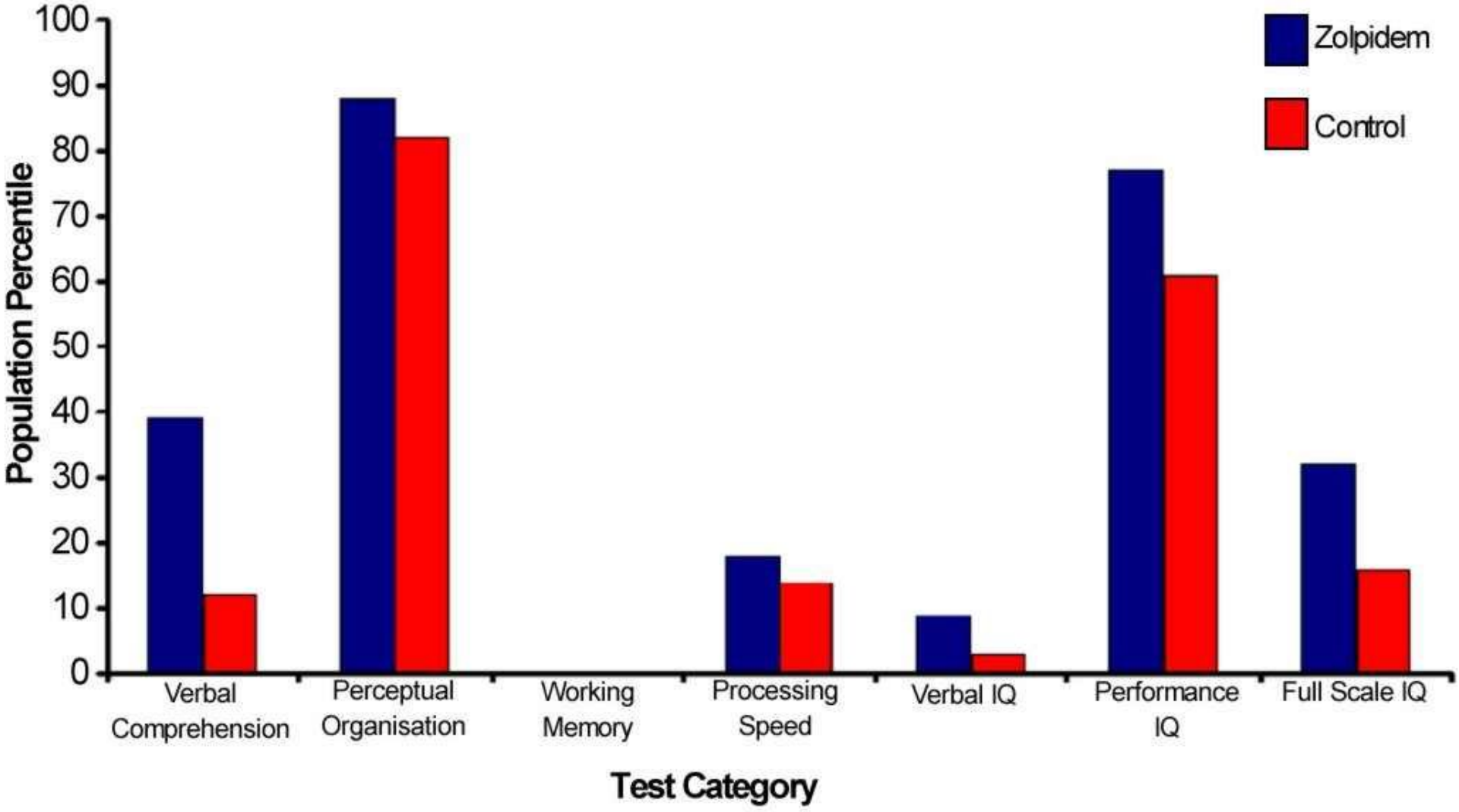
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Performance IQ
Full Scale IQ
Test Category