



Functional neural networks of time perception: Challenge and opportunity for schizophrenia research

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ARTICLE INFO

Article history:

Received 4 May 2010

Received in revised form 7 September 2010

Accepted 5 October 2010

Available online 1 November 2010

Keywords:

Schizophrenia

Time-estimation

Timing

Cognition

Neuroimaging

fMRI

PET

Workingmemory

Meta-analysis

ABSTRACT

With the double objective of searching for a physiological brain circuit concerned with time estimation and establishing whether this circuit is dysfunctional in schizophrenia patients, we carried out an activation likelihood estimate (ALE) meta-analysis of published functional neuroimaging studies.

Our results reproduce the previous finding of a neurophysiological cortico–cerebellar–thalamic circuit related with time estimation in healthy individuals. In schizophrenia patients, the analysis indicates significantly lower activation of most right hemisphere regions of the circuit, suggesting that it may be subject to a pattern of disconnectivity.

The ALE-meta-analysis approach is useful and further studies could elucidate how the timing circuit is connected with other cognitive tasks.

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1. Introduction

In the last five years, neuroscience research in the area of time perception has focused particularly on the functional mechanisms of interval timing and has highlighted the functional role of the motor and supplementary pre-motor area, as part of the thalamo–cortico–striatal circuits (Basso et al., 2003; Buhusi and Meck, 2005; Nachev et al., 2008; Mita et al., 2009).

The timing task and its neural networks may be of great relevance in healthy cognition as they are apparently related to several other functions such as attention and working memory (Buhusi and Meck, 2005). It has been proposed that the connection stems from the involvement not only of cortical structures such as the dorsolateral prefrontal cortex that play a well-known role in normal cognitive functions but also of other regions, such as the supplementary and pre-

supplementary motor areas, which have recently been identified as crucial for linking cognition to action (Basso et al., 2003).

From a phenomenological and neuroscientific perspective, schizophrenia can be regarded as a structural disturbance of time consciousness (Vogelei and Kupke, 2007). In view of the relationship between time perception and other cognitive domains, there has recently been increased interest among neuropsychological researchers of schizophrenia in the study of time perception. Using various procedures, schizophrenia patients have been shown to have less ability to judge correctly the temporal-order (Braus, 2002) or precise duration of visual or acoustic stimuli (Carrol et al., 2008).

Structural neuroimaging studies have related cognitive symptoms in schizophrenia with the most prominent morphological abnormalities detected, those in the dorsolateral and orbitofrontal cortex. To our knowledge, only one study has found schizophrenia patients to have smaller left pre-supplementary motor area volumes relative to control subjects. Interestingly, in that study the size of this region was

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correlated with ability at sequence-implicit motor learning (Exner et al., 2006).

There are many functional neuroimaging studies of time perception in people with normal cognition, but, to our knowledge, there is only one meta-analysis that uses the activation likelihood estimation algorithm to evaluate voxel-based studies in healthy individuals in order to determine which structures are relevant to interval timing (Wiener et al., 2010). That study focused on two dimensions: stimulus duration (sub- vs. supra-second) and the nature of response (motor vs. perceptual) and determined the existence of dissociable neural networks for the processing of duration with motor or perceptual components.

In contrast to the aforementioned meta-analysis, that reported here is centered on cerebral circuits related to both explicit and implicit time estimation tasks. According to the classification of timing by Coull and Nobre (2008), explicit timing tasks require subjects to provide an overt estimate of duration. For example, subjects must state whether the duration of one stimulus is shorter or longer than another one. Implicit timing, on the other hand, is engaged as a means to achieve tasks that are primarily non-temporal but nevertheless involve sensory stimuli that adhere to a strict temporal framework. For example, subjects are required to make a perceptual judgment about stimulus features or to perform a specific motor act.

There are few published studies of time estimation in schizophrenia. Our own O_{15} -water PET studies of schizophrenia patients suggest that during auditory attention and whilst performing time estimation tasks there is a dysfunctional pattern, with underactivity of the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC) and parietal cortex (Ojeda et al., 2002; Ortuño et al., 2005).

In order first to examine the regions engaged in a physiological time estimation circuit, and second, to test whether patients with schizophrenia show a dysfunctional activity pattern in this circuit, we conducted an activation likelihood estimate (ALE) meta-analysis of published neuroimaging data.

2. Methods

ISI Web of Science and Medline databases were searched up to March 2010 using the keywords *positron emission tomography** and *functional magnetic resonance imaging** cross-referenced with *time estimation**, *timing** OR *time perception**, where * indicates a wild-card. For the second meta-analysis, a further search was conducted in which *positron emission tomography** and *functional magnetic resonance imaging** were cross-referenced with *schizophrenia**.

Papers were selected following selection criteria of a similar ALE meta-analysis previously conducted by Petacchi et al. (2005) (Table 1).

Tailarach coordinate space data from the studies were imported into ALE software developed at the Research Imaging Center (online at <http://www.brainmap.org/ale>). The Tailarach space was divided into cubic voxels of 2 mm. A whole-brain ALE map was created by modeling the foci as localization probability distributions centered at the coordinates of each voxel. The probability of each focus being located within a voxel was calculated with a 3D Gaussian function of 12 mm full-

Table 1
Inclusion criteria.

Studies should have been published in a peer-review journal.
They had to report the coordinates of activation maxima in a standardized stereotaxic space.
All brain areas should had been analyzed for activation, not just regions of interest.
Only studies of healthy individuals and only comparative studies with schizophrenia were included for the first and second meta-analysis, respectively.
Studies should include at least one contrast of explicit or implicit timing. Stimuli could be either auditory (i.e. listening to rhythm, tones, clicks) or visual (words, numbers).
Studies including motor tasks, (i.e. finger tapping, loud counting) should control movement by subtraction between conditions.

width half-maximum (FWHM). The ALE value was computed as the sum of the Gaussian probabilities derived from all studies. The threshold of statistical significance was established by means of a permutation test of randomly generated sets of foci. Detailed description of the ALE method and the statistical test employed can be found in Turkeltaub et al. (2002) and Laird et al. (2005). We used MRICron software to visualize ALE maps overlaid onto a high-resolution brain template generated by the International Consortium for Brain Mapping (Kochunov et al., 2002).

We ran two ALE analyses of studies in healthy subjects: one including both studies of explicit or implicit timing tasks and another of explicit timing studies alone. A third analysis covered studies comparing healthy subjects and schizophrenia patients on time estimation tasks.

3. Results

The normal-case meta-analysis comprised 35 articles (13 for implicit timing tasks and 22 for explicit tasks). We found only three articles investigating time perception in schizophrenic subjects. Two of these articles concerned our own PET studies (Ojeda et al., 2002; Ortuño et al., 2005) and the third was an fMRI study done by another group (Volz et al., 2001). All three investigated explicit timing tasks in patients with schizophrenia (Table 2). A total of 477 foci were analyzed in the former meta-analysis, and 10 in the latter.

The normal-case meta-analysis confirmed the neurophysiological finding that time perception significantly activates the frontal (BA: 6,8,9,10), parietal (BA: 7, 40), and temporal (BA: 22, 37, 41) regions and the putamen, thalamus and cerebellum (Table 3, Fig. 1). Analysis of those results that related to explicit time estimation alone identified similar activation clusters to those found when implicit task results were included (Table 4).

The meta-analysis of the results with schizophrenic subjects showed, relative to healthy subjects, significantly lower activation of the right frontal regions: the right precentral gyrus (BA 6); the superior (BA 9) and middle (BA 8 and 10) frontal gyrus; left anterior cingulate (BA32) the right parietal cortex (BA 39); and the right putamen and the thalamus ($p < 0.05$) (Table 5, Fig. 2).

4. Discussion

It is now over a decade since Andreasen (1999) proposed study of time estimation in schizophrenia to discover more

Table 2

Studies of temporal processing included in our meta-analysis.

Author	n	Neroimaging tool	Experimental time estimation task	Timing
<i>Studies in healthy subjects</i>				
Bengtsson et al., 2009	17	fMRI	Auditory rhythm perception: more vs. less complex	I
Botzung et al., 2008	10	fMRI	Past vs. future no external stimuli	I
Tsukamoto et al., 2006	20	fMRI	Visual stimuli. Prediction of duration	I
Dudukovic and Wagner, 2007	18	fMRI	Visual stimuli (nouns): recent vs. new	I
Knutson et al., 2004	19	fMRI	Visual stimuli: the script order task vs. the chronological order task	I
Rekkas et al., 2005	10	fMRI	Visual stimuli: autobiographic temporal-order vs. autobiographic spatial location, semantic temporal-order, and semantic spatial location.	I
Basso et al., 2003	5	fMRI	Estimation of digits duration: more vs. less complex	I
Beudel et al., 2009	18	fMRI	Visual stimuli: prediction of position of a ball vs. previous learned trajectory	I
Coull and Nobre, 1998	7	fMRI and PET	When vs. where of visual stimuli	I
Coull et al., 2000	6	fMRI	Estimation of when appear a visual	I
Ackermann et al., 2001	8	fMRI	Isochronous trains of clicks of passive listening to different frequencies of clicks	I
Berns et al., 1997	10	PET	Passive viewing numbers, not knowing that they are series)	I
Schubotz and von Cramon, 2001	12	fMRI	Order estimation visual forms	I
Lewis et al., 2004	10	fMRI	Auditory tone: continue a learned finger tapping task)	E
Livesey et al., 2007	10	fMRI	Duration of visual stimuli vs. colour discrimination	E
Ortuno et al., 2002	11	PET	Mentally and silence counting vs. auditory clicks rhythm counting	E
Pouthas et al., 2005	6	fMRI	Visual letters duration exposition	E
Neufang et al., 2008	34	fMRI	Visual stimuli vs. time discrimination	E
Rao et al., 2001	17	fMRI	Auditory time pitch discrimination	E
Harrington et al., 2004	24	fMRI	A time duration discrimination of visual stimuli	E
Stevens et al., 2007	31	fMRI	Three timing tasks (synchronize, syncopate, and listen) vs. three rates of previous learned auditory cues presentation	E
Brunia et al., 2000	8	PET	Visual signs, estimation anticipatory of early or late presentation	E
Mathiak, 2004	12	fMRI	Auditory tones discrimination of time duration	E
Maquet et al., 1996	9	PET	Estimation of duration of visual stimuli vs. intensity task	E
Macar et al., 2004	13	fMRI	A time production and a force production task	E
Lux et al., 2003	14	fMRI	Visual estimation of appearance of two rhombus simultaneous vs. position	E
Lewis et al., 2004	10	fMRI	Continue a learned finger tapping task vs. listened: three levels of rhythm difficulty	E
Jantzen et al., 2005	12	fMRI	Continue a learned finger tapping task vs. listened	E
Ferrandez et al., 2003	11	fMRI	Visual discrimination of duration of stimuli (same as Maquet et al., 1996).	E
Karavanov et al., 2009	16	fMRI	Visual and auditory learned rhythms	E
Schubotz and von Cramon, 2001	12	fMRI	Visual and auditory rhythms deviations	E
Rubia et al., 1998	6	fMRI	Visual stimuli synchronization delay vs. synchronize	E
Tregellas et al., 2006	20	fMRI	Auditory tones discrimination of duration	E
Pastor et al., 2004	14	fMRI	Temporal discrimination 1 or 2 clicks vs. location right or left	E
Schubotz et al., 2000	20	fMRI	Visual and auditory Time estimation of stimuli	E
<i>Studies in schizophrenia vs. healthy subjects</i>				
Volz et al., 2001	8	fMRI	Auditory time estimation vs. frequency (i.e. pitch) discrimination task vs. rest	E
Ojeda et al., 2002	11	PET	Mentally and silence counting vs. auditory clicks rhythm counting	E
Ortuno et al., 2005	10	PET	Mentally and silence counting vs. auditory clicks rhythm counting	E

I: implicit timing. E: explicit timing. fMRI: functional magnetic resonance imaging. PET: positron emission tomography.

about the core symptoms of this disorder, which she termed “cognitive dysmetria,” and the underlying disorder in the cortico-cerebellar-thalamic-cortical circuit. The results of this meta-analysis confirm the involvement of a neurophysiological cortical-subcortical circuit related with time estimation. With regard to the regions involved, the findings coincide with those of Wiener et al.’s (2010) meta-analysis for perceptual timing: that the bilateral supplementary motor area (BA6); the right middle (BA 9,10) frontal and the right inferior parietal (BA40) regions; and the right insula, the left putamen participate in time estimation. Additionally, we found the implication of other regions: the left insula, the right posterior cerebellum, the superior temporal gyrus and the right thalamus, the right middle frontal gyrus, and the left superior temporal gyrus. All of these regions have previously

been confirmed to constitute parts of the neural timing circuit (Stevens et al., 2007).

As in the Wiener et al. (2010) study, it was notable in our study that the SMA contained one of the greatest numbers of significant ALE voxels whether analyzing studies of explicit timing tasks alone or both explicit and implicit tasks. Since explicit timing tasks are perceptual and non-motor tasks, the implied involvement of the SMA is related to specifically cognitive demands of time estimation rather than with motor activation.

Whilst the role of this area is traditionally seen to be purely motor oriented, a recent review considers that BA6 may be activated by demand for implementation of several cognitive tasks: mental arithmetic, spatial and non-spatial working memory, attention control, silent work production

Table 3

Significant activation likelihood clusters of time estimation tasks in studies of healthy subjects.

Label	Volume mm ³	x	y	z	ALE
Insula.BA 13 R	13,664	33.12	12.2	7.52	0.045
Medial frontal gyrus BA6 L	13,360	-0.01	4.54	55.67	0.047
Precentral gyrus.BA 6 L	7984	-37.83	-2.06	48.96	0.034
Lentiform putamen L	3760	-20.92	4.29	7.39	0.032
Inferior frontal gyrus.BA44 L	3112	-49.62	9.37	11.59	0.024
Inferior parietal lobule BA 40 R	2320	39.04	-44.65	41.2	0.036
Middle frontal gyrus BA6 R	2232	45.17	4.75	44.07	0.020
Inferior parietal lobule.BA 40 L	1936	-39.5	-46.3	45.66	0.028
Thalamus medial Dorsal Nucleus R	1568	6.95	-15.25	5	0.022
Insula BA 13 L	1312	-34.21	17.13	-1.64	0.022
Middle frontal gyrus. BA 6 R	976	24.54	-3.23	50.05	0.024
Middle frontal gyrus BA 9 R	536	51.29	21.8	28.2	0.021
Inferior parietal lobule. BA 40 R	440	51.57	-31.55	46.39	0.016
Superior frontal gyrus BA 10 L	416	-35	49.6	17.27	0.018
Cerebellum posterior lobe. Declive R	352	20.82	-56.1	-12.17	0.019
Middle temporal gyrus.BA37 L	256	-48.16	-62.35	6.38	0.017
Insula.BA 13 L	168	-45.9	-40.94	22.36	0.017
Superior temporal gyrus. BA 41 L	160	-57.96	-26.51	8.02	0.017
Parietal lobe.Precuneus.BA 7 R	160	9.79	-67.78	45.7	0.017
Superior frontal gyrus.BA 10 R	136	34.14	47.06	23.04	0.015
Parietal lobe. Precuneus. BA 7 L	128	-10.73	-66.25	50.1	0.016
Inferior frontal gyrus.BA 10 L	120	-46.86	42.83	-0.7	0.014
Cerebellum anterior lobe. R	112	27.14	-55.3	-28.03	0.016
Thalamus L	112	-11.02	-20.66	8.02	0.015

and conceptual reasoning (Hanakawa et al., 2008). Our results imply BA6 has a key function in temporal cognition.

Several studies utilizing electroencephalography (EEG) and magnetoencephalography (MEG) have also revealed ramp-shaped contingent negative variation over the SMA during timing tasks (Macar and Vidal, 2002; Pfeuty et al., 2003; Noguchi and Kakigi, 2006), leading the respective authors to hypothesize that the SMA serves as a temporal accumulator.

With regard to the physiological time estimation network in schizophrenic subjects, our meta-analysis demonstrates that the participation of most of the cortical and subcortical regions primarily in the right hemisphere is reduced relative to healthy subjects. This finding suggests that a pattern of disconnectivity of the time estimation circuit is a characteristic of the schizophrenic condition. Note, in particular, the implication of a dysfunction in the BA6 region (which contains pre-SMA and SMA), a finding that introduces a more or less novel notion in the field of schizophrenia research.

The additional dysfunctional regions identified by our meta-analysis in schizophrenia belong to the functional neural circuits for time perception: the right lentiform nucleus and thalamus are active during time estimation tasks (Rao et al., 2001). The superior frontal (BA 9 and 10) plays a special role in holding temporal intervals (Rubia and Smith, 2004). The middle frontal gyrus (BA8), the cingulate gyrus (BA32), the posterior parietal region (BA39), and the right parietal precuneus (Ojeda et al., 2002) are important for sustained attentional components of time estimation.

The idea that in the healthy mind regions of both hemispheres participate in time estimation concurs with evidence from neurophysiological studies, both classic and recent, on reaction time and motor tasks (Ringo et al., 1994; Barnett et al., 2005). Our results suggest that there is a failure of inter-hemispheric cooperation in response to timing tasks in schizophrenia and that the right hemisphere is predominantly involved. A lack of inter-hemispheric cooperation has

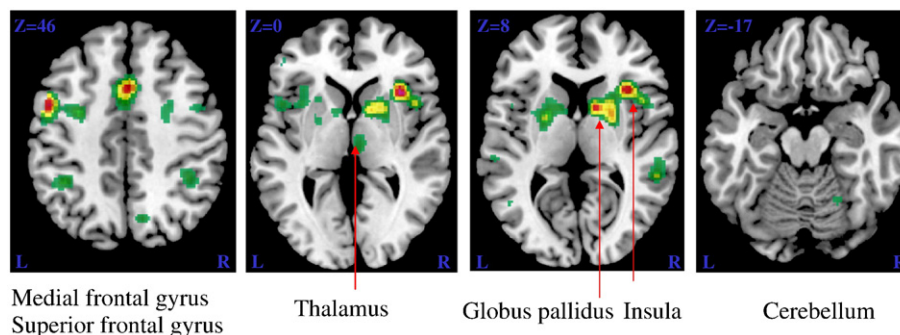


Fig. 1. ALE maps of time estimation (studies of healthy samples).

Table 4

Significant activation likelihood clusters of explicit time estimation tasks in studies of healthy subjects.

Label	Volume mm ³	x	y	z	ALE
Insula.BA 13 R	13,368	34	20	4	0.037
Medial frontal gyrus BA6 L	12,416	-2	-4	56	0.041
Precentral gyrus.BA 6 L	5816	-48	2	46	0.032
Lentiform putamen L	3248	-22	0	8	0.018
Inferior frontal gyrus. BA 40 R	3112	38	-44	40	0.035
Inferior parietal lobe BA 44 L	1920	-50	10	20	0.019
Inferior parietal lobe BA 40 R	1088	-38	-46	48	0.018
Superior temporal gyrus BA 22 R	1040	56	-40	8	0.019
Insula BA 13 L	1040	-36	14	-2	0.017
Middle frontal gyrus. BA 6 R	904	24	-4	50	0.022
Thalamus R	880	4	-20	0	0.018
Middle frontal gyrus BA 6 R	536	44	0	50	0.014
Cerebellum posterior lobe. Declive R	440	22	-58	-12	0.018
Parietal lobe. Precuneus. BA 7 R	256	10	-62.35	6.38	0.016
Insula.BA 13 L	168	-46	-40	22	0.016
Middle frontal gyrus.BA 8 R	128	52	12	40	0.012
Superior temporal gyrus BA 42 L	112	-58	-28	8	0.012

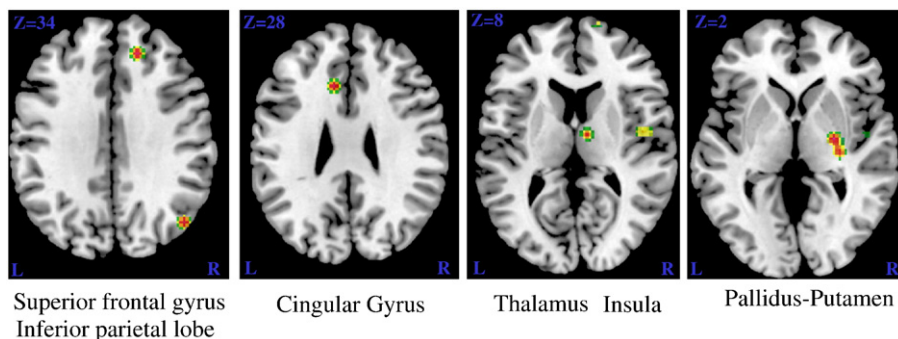
Table 5

Significant activation likelihood clusters for time estimation tasks: differences between healthy samples and schizophrenia patients.

Location	Volume mm ³	x	y	z	ALE
Lentiform nucleus (R)	1408	28	-14	0.89	0.007
Precentral gyrus.BA6 (R)	1208	48	-6	5.66	0.008
Superior frontal gyrus.BA9 (R)	560	16	38	34	0.006
Parietal lobe.Precuneus.BA39 (R)	504	46	-70	34	0.007
Thalamus (R).	488	8	-7	11	0.006
Cingulate gyrus.BA 32 (L)	392	-9	24	28	0.007
Middle frontal gyrus. BA 8 (R)	224	36	36	40	0.006
Superior frontal gyrus. BA 10 (R)	128	14	66	8	0.005

already been proposed in neuropsychological (Barnett et al., 2005) and neurophysiological (Mohr et al., 2008) studies of language processing in schizophrenia. Together with the aforementioned regions of the timing circuit, specific pathways of the corpus callosum responsible for inter-hemispheric coordination (Ringo et al., 1994) might also be relevant to normal time perception. Thus, certain abnormalities in the corpus callosum that have been described in schizophrenia (Highley et al., 1999) might be implicated in timing dysfunction in this disorder.

We emphasize that ALE-meta-analysis of neuroimaging studies of healthy and schizophrenic people is adequate to the task of testing the relationships between neural structures of timing and those of higher functions. Our emerging hypothesis is that timing structures are activated either by increased demand on working memory, by the need to shift attention from lower automatic levels to higher controlled levels, or in response to certain complex mental operation tasks. Thus, a dysfunctional time estimation network may be linked with other critically impaired functions in schizophrenia.

**Fig. 2.** ALE maps of time estimation studies (schizophrenia < healthy subjects).

Role of funding source

This work was partially supported by a grant, awarded in July 2010, from the Department of Health of the Government of Navarra (Spain).

Contributors

F.O. wrote the manuscript, F.G.-G. and J.G. conducted the data analyses, P. L-G and J.P. supervised the project.

Conflict of interest

All authors of this work declare not to have any actual or potential conflict of interest.

Acknowledgements

We thank Eduardo Ortuño for his assistance in data analysis.

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