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# Frequency-dependent enhancement of fluid intelligence induced by transcranial oscillatory potentials

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Summary

Everyday problem-solving requires the ability go beyond experience, by efficiently encoding and manipulating new information, i.e. fluid intelligence (f*g*) (Horn and Cattel, 1966). Fg usually declines with physiological aging and contributes to the functional impairment of many chronic-degenerative neurological conditions (Yoshura et al. 2011, Morrison et al. 2004), showing at the same time a resilience towards influences of education, socialization, drugs and behavioral training (Weng-Tink Chooi et al. 2012; Gray et al. 2004). Performance in tasks involving fg-related cognitive functions, such as logical abilities and abstract reasoning, has been shown to rely on aneural networks with a crucial role played by specific prefrontal regions, such as the middle frontal gyrus. Synchronization of neuronal activity in the gamma band havebeen suggested to be a ubiquitous mechanism for the orchestration of distributed activity in the brain, possibly subserving cognitive functions. However, no evidence of its causal involvement exists to date. Here we provide the

first evidence of enhancement of performance in a cognitive task by exogenous stimulation in the gamma band. Weak alternated current (Kanai et al. 2008) applied through the scalp over the left middle frontal gyrus resulted in a frequency-specific reduction of reaction times in a a visuo-spatial abstract reasoning task, classically employed to index *fg* abilities (Matzen et al. 2010), Gamma-band stimulation selectively enhanced performance on more complex trials, involving conditional reasoning and logic. The observed transitory improvement of fg in healthy humans suggests new rehabilitative approaches in pathological conditions. Additionally, contrasting with the view of high frequency synchronization as a simple epiphenomenon of neuronal activity (Jia et al. 2011), the present finding provides evidence supporting a more direct involvement of gamma oscillatory activity in the mechanisms underlying human cognition.

## Letter

When facing novel situations, the accurate retrieval of information from past experience could be useless, and even everyday life problems unsolvable unless we capture new relations between objects , and promptly extrapolate correct solutions through logic abilities. Such crucial, experience-independent, components of human cognition -globally referred as fluid reasoning or intelligence (f*g*) (Horn and Cattel, 1966)- are fundamental in encoding efficiently new information, which successively can be exploited as a crystallized form of intelligence (*cg*). As a matter of fact, *fg* has been shown to positively correlate with performance in a wide range of cognitive tasks, and to be an important predictor of both educational and professional success (Baltes et al. 1999).

Fluid intelligence, as other cognitive resources, usually declines with physiological aging and, even more, when pathological processes overlap; hence, its decline contributes to the dramatic functional impairment of many chronic-degenerative neurological conditions (Yoshura  et al. 2011, Morrison et al. 2004).

However, such vulnerability contrasts with the resilience of *fg* towards influences of education, socialization, pharmacological interventions (e.g. stimulants) and behavioral training (Chooi et al. 2012; Gray et al. 2004) making it a key, but still missed, target for cognitive neurorehabilitation.

Neuroimaging and experimental evidence indicate a limited number of brain areas supporting logical abilities: abstract reasoning tasks are associated with different levels of activations in frontal and parietal areas, with frontal involvement increasing with task difficulty (Jung and Haier, 2007; Duncan et al., 2000). Indeed, after initial engagement of parietal regions, believed to mainly sustain perceptual processing, the online manipulation of information is accompanied by specific prefrontal activations (Koechlin et al., 2003, Houdé et al., 2003, Krawczyk, 2012). However, fluid reasoning should be regarded as a heterogeneous construct, with performance in specific tasks subserved by partially distinct structures: prefrontal activation is crucial in tasks involving conditional arguments (e.g. Modus Tollens: if P then Q; not-Q), while other tasks involving the formulation of Relational Syllogisms (e.g. P is to the left of Q; Q is to the left of R) seem to rely on posterior areas, such as the temporo-parietal-occipital junction (Prado et al. 2010). Among prefrontal regions, a prominent role has been assigned to the left middle frontal gyrus (MFG), which seems to support abstract reasoning by integrating logical relationships and inhibiting irrelevant information during falsification processes (Liu et al. 2012). MFG appears therefore to be a key component of a processing module that sustains performance in a largely modality-independent manner -its activation has been reported in both visuo-spatial and verbal analogical reasoning tasks (Krawczyk et al. 2011)-, when tasks requires to move beyond perceptual relations through complex abstraction.

Neurophysiological investigations with higher temporal resolution (i.e. EEG/MEG) have provided additional insights into the cortical underpinnings of higher order cognition, and highlighted the importance of synchronized activity in the 30-80 Hz electroencephalographic band, i.e. the gamma rhythm. To date its involvement in abstract reasoning hasn't been directly assessed. However since gamma activity appears to be an ubiquitous mechanism in large scale coordination of distributed activity associated with a wide range of mental operations, (attention (Tallon-Baudry et al., 2005), memory (Howard et al. 2003), language (Bastiaansen and Hagoort, 2006), learning (Bauer 2007)), it might also be involved in the orchestration of prefrontal activity related to fluid intelligence. Therefore, while anatomical and neurometabolic studies support the key role played by left prefrontal areas - and by MFG in particular - in fluid reasoning, neurophysiological evidence suggests that such involvement can possibly be indexed by oscillatory gamma-band activity.

In this context we aimed to improve *fg* in healthy subjects, by using a recent neuromodulatory technique called Transcranial Alternating Current Stimulation (tACS), a non-invasive brain stimulation method shown to be effective in the frequency specific modulation of regional cortical activity. The application through the scalp of alternating weak currents it has been suggested to affect endogenous brain rhythms (*entrainment* phenomenon; Thut and Miniussi 2008; Thut et al. 2012), thereby modulating the functions associated with synchronized activity in the underlying cortex (Marschall et al., 2006, Paulus, 2010). This phenomenon has been described for the motor (Feurra et al. 2011, Pogosyan et al. 2009), visual (Kanai et al. 2008) and somatosensory (Feurra et al. 2011) domains, and initial evidence supports its involvement in higher functions, such as working memory (Polania et al. 2012).

Twenty healthy volunteers underwent left MFG tACS while performing a modified version of Raven's Matrices (Matzen 2010), which allowed repeated assessments of performance in this classic test *fg* abilities. We assessed reaction times (RT) (i.e., the time to solve each matrix) and accuracy in trials of increasing complexity that tackled relational and conditional, logic abstract reasoning (namely, matrices with 1, 2 or 3 relations, or logic trials. ). Based on the previous functional assumptions, we aimed to "entrain" main physiological brain rhythms with four conditions of tACS - 5 Hz (θ band), 10 Hz ($\alpha$ band), 20 Hz ($\beta$ band), 40 Hz ($\gamma$ band) - and compared performance with a placebo, sham condition. Details about experimental procedures and tACS parameters are reported in Fig. 1 (see also supplemental materials).

A definite frequency-specific effect emerged, as performance was significantly affected only by $\gamma$-tACS of the left MFG. Most importantly, these effects were specific to conditional reasoning (i.e. to logic fg trials). The overall pattern of accuracy and RTs was consistent with the involvement of at least partially separable resources in the solution of the two different types of trials, validating previous assumptions about the role of the MFG in specific components of fg. The longer RTs required to solve logic matrices (Fig 1 A) cannot be accounted by a greater difficulty along the same dimension: no correlation was observed between RT in the two subtasks (logic vs 3 relations: $r=.12$, n.s.), while individual performance in increasingly difficult relational tasks was highly correlated (1 vs 2 relations: $r=.81$; 1 vs 3 relations, $r=.69$, $p<.001$, fig.1B). We observed that error rates were less effective in differentiating subtests, with comparable accuracy in logic and most difficult relational trials, together with overall increased shared variability.

The time required to produce correct responses was consistently affected by $\gamma$-tACS in a trial type specific manner. Regression analysis (Generalized Estimating Equations, gamma distribution, loglog link, Ballinger 2004) where tACS conditions and trial type were predictors yield to an highly significant estimation of the interaction terms (tACS*trial type $\chi 2=42.2$, $p<.001$; tACS $\chi 2=4.15$, $p=.386$; task $\chi 2=1614.72$, $p<.001$). Pairwise comparisons of active tACS vs sham conditions highlighted the source of interaction being faster RT in the logic subtest during $\gamma$-tACS (the only significant difference, mean difference= -3.2s, $p=.001$, fig.2 A and B). Analysis on errors did not show significant interactions (logistic regression: tACS*task $\chi 2=12.7$ $p<.122$; tACS $\chi 2=1.84$, $p=.786$; task $\chi 2=138.68$, $p<.001$), nor pairwise differences. Most importantly, $\gamma$-tACS appeared to improve logic processing speed, rather than changing speed-accuracy trade-off: parametric analysis on RT for error trials did not lead to significant differences. This observation was confirmed by inspection of empirical distributions (Fig. 2, C) and by not parametrical approaches which showed that the likelihood of a response faster than the median RT to be correct did not differ across tACS conditions (aside of a not significant tendency of fast responses in tACS at 40Hz and 10Hz to be more likely to be accurate; tACS $\chi^2$=4.8, p=306). Additionally, the effects of $\gamma$-tACS showed an inverse correlation with performance on baseline (sham) condition (Fig.2D), suggesting that the magnitude of gamma-rhythm entrainment on cognition may proportionally respond to a physiological need (see supplemental materials for detailed statistical procedures and additional results). This opens intriguing scenarios for cognitive rehabilitation in pathological conditions.

One single application of tACS transiently improved logic reasoning speed. Such finding in healthy subjects suggests a new area of investigation in the cognitive rehabilitation of fluid reasoning, which usually declines in physiological aging and is worsened by many pathological processes, but is largely unaffected by available approaches. Moreover, the modulation of a cognitive function associated to gamma activity raises the possibility to target a wider range of functions. Accordingly, either neurological conditions (e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis) or developmental disorders (e.g. ADHD) where cognitive impairment has been suggested to be related to gamma disturbances, could represent future research areas.

The reported study extends to the cognitive domain observations of modulation of activity by tACS in corticospinal, visual and sensory systems (Feurra et al. 2011, Kanai 2008, Pogosyan, 2009). While the definitive demonstration of entrainment as the mechanism underlying tACS effects relies on overcoming technological constraints, such findings are interpreted as evidence of frequency-specific modulation of endogenous rhythms. In this light the present finding can represent an advance in the understanding of the neural mechanisms underlying fg, and the relationship between high frequency oscillations and cognition, and suggests synchronization to be causally involved in mental operation instead of mere byproduct of neuronal activity (Jia, 2011).

**Fig 1. TASK, STIMULATION AND PERFORMANCE.**

(A.) Each matrix was composed by an upper part containing a 3x3 stimuli grid. Subjects were asked to report which of 8 objects listed underneath would complete the series by filling the bottom right blank cell. The correct response could be inferred either capturing *relations* across objects, i.e. the one, two or three features along which objects varied across the matrix or performing *logic* operations (i.e. conjunction, disjunction, or exclusive disjunction) across the grid.

(B) Stimulating electrodes were positioned according to the International 10-20 EEG System: the "active" electrode was centered on left middle frontal gyrus [x=-34,y=16,z=30], whereas the "reference" electrode was placed on Cz (vertex).

(C) During each tACS condition accuracy and reaction times were acquired for 12 matrices of each of the 4 type, randomly presented. A maximum of 60 s. were allowed to solve each matrix. A resting period (20') was allowed between presentations, during which subjects performed a low load disengaging task without stimulation.

(D) Mean error rates and accurate response times. Logic reasoning is a costly process: in order to match the accuracy observed in the solution of 3 relations tasks, the solution of logic subtests appears to require longer reaction times [raw means (+- se)].

(E) Data-driven relations across trial types. Principal component analysis offers a straightforward depiction of the observed correlation structure (unrotated solution, analysis on correlation matrix): the orthogonal distribution for relational and logic subtests suggests that individual variability in reaction times arises from heterogeneous processes across tasks. For mean error rates a higher correlation along the first component was observed (coefficients for all variables >4, logic and 3 relations raw correlation: $r=.46$, $p=0.032$).

**Fig 2. tACS EFFECTS.**

(A) tACS vs SHAM: T score. Reaction times on accurate were significantly faster when subjects received □(40Hz)-tACS specifically in the solution of matrix involving logic reasoning. No difference from sham stimulation was observed in the extrapolation of relational rules (pairwise comparisons of transformed accurate response times tACS vs sham, *p=.001, corrected). Accuracy did not differ across conditions (lower raw).

(B) Mean reaction times for accurate responses in logic trials across tACS conditions. On the y-axis mean reaction times in the 4 different trial types are shown for reference. During □(40Hz)-tACS reaction times appear to be half a way between responses in 3 relations trials and in logic matrices without stimulation.

(C) Empirical cumulative distribution of reaction times. The effect of tACS does not appear to derive from changes in speed-accuracy tradeoff, as wrong responses appear to be unaffected by stimulation.