European Neuropsychopharmacology (2016) **26**, 1255–1263

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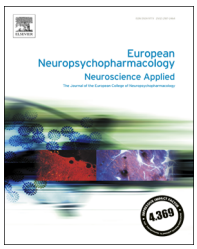

Prefrontal inositol levels and implicit decision-making in healthy individuals and depressed patients

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Received 18 January 2016; received in revised form 16 April 2016; accepted 1 June 2016

KEYWORDS
Spectroscopy;
Depression;
Decision-making;
Inositol;
Learning

Abstract
Risky decision-making is found in several mental disorders and is associated with deleterious consequences. Current research aims at understanding the biological underpinnings of this complex cognitive function and the basis of individual variability. We used 3 T proton Magnetic Resonance Spectroscopy to measure in vivo glutamate, GABA, N-acetyl-aspartate (NAA), and myo-inositol levels at rest in the right dorsal prefrontal cortex of 54 participants, comprising 24 unmedicated depressed patients and 30 healthy individuals. Participants were also tested with the Iowa Gambling Task (IGT), a classical measure of value-based decision-making. No group differences were found in terms of compound levels or decision-making performance. However, high inositol levels were associated with lower decision-making scores independently from group, notably during the initial stage of the task when explicit rules are still unknown and decisions are largely based on implicit processes (whole sample: $F=4.0$; $p=0.02$), with a large effect size (Cohen's $d=0.8$, 95% [0.2–1.5]). This effect was stronger when explicit knowledge was taken into account, with explicit knowledge showing an independent effect on performance. There was no association with other compounds. This study suggests, for the first time, a role for the inositol pathway on the implicit learning component of decision-making, without any direct effect on the explicit component. Hypothesized mechanisms implicate intracellular calcium modulation and subsequent synaptic plasticity. These findings represent a first step in

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http://dx.doi.org/10.1016/j.euroneuro.2016.06.005

the understanding of the biochemical mechanisms underlying decision-making and the identification of therapeutic targets. They also emphasize a dimensional approach in the study of the neurobiological determinants of mental disorders.

1. Introduction

In our lives, we have to make countless decisions. One study showed that just for food, more than two hundred decisions have to be made each day (Wansink and Sobal, 2007). Human capacity has uniquely evolved to make decisions under uncertain and complex conditions, integrating the memory of past experiences, current internal and external information, and anticipated outcomes (Bechara et al., 1997; Ernst and Paulus, 2005; Kahneman, 2011). While efficient decision-making is critical for adaptation and success in life, individual variability in decision-making capacities is obvious.

Some people tend to repeatedly choose options with immediate rewards, regardless of the long-term negative consequences, which often yield deleterious outcomes at the social, marital, professional and financial levels (Bechara et al., 1994). For instance, risky decision-making is correlated with more interpersonal difficulties (Jollant et al., 2007b), more social disturbances (Bar-On et al., 2003), a tendency for recidivism in legal offenders (Beszterczey et al., 2013; Bouchard et al., 2012), or repeated impulsive aggression (Best et al., 2002). Impaired decision-making is found in patients with particular brain lesions (Bechara et al., 1994), but also in several mental disorders including alcohol and substance abuse (Bechara et al., 2001), bipolar disorder (Adida et al., 2011), and personality disorders like psychopathy (Beszterczey et al., 2013) or borderline personality disorder (Bazanis et al., 2002), among others. There is also evidence that compromised mechanisms of decision-making increases the risk of suicidal acts among depressed patients (Jollant et al., 2005; Richard-Devantoy et al., 2014). Hence, understanding the mechanisms of decision-making will shed light on potential therapeutic targets and intervention strategies.

The biochemical underpinnings of decision-making are not well known. Although the neuromodulators serotonin and dopamine (Rogers, 2011), or the hormones cortisol (van den Bos et al., 2009) and testosterone (van Honk et al., 2004), have all been linked to neural mechanisms involved in decision-making, less is known about the implication of the major ubiquitous neurotransmitters Glutamate and GABA. Jocham et al. (2012) found that GABA levels in ventromedial prefrontal cortex were positively correlated with decision-making accuracy, while glutamate levels were inversely correlated. Fujihara et al. (2015) found that GABA levels in perigenual anterior cingulate cortex were negatively correlated with delay aversion, while (Glutamate+Glutamine) levels were inversely correlated with risk adjustment measured by the Cambridge Gamble Task. In this latter study, reported levels were not correlated with final performance, suggesting that the measured neurochemicals only encode particular aspects of decision-making. Other brain regions and sub-processes have now to be explored.

Apart from glutamate and GABA, we were also particularly interested in the link between decision-making and certain markers of cellular functioning, including N-acetyl-aspartate (NAA) a marker of neuronal integrity, and myo-inositol (Bittsansky et al., 2012). Regarding inositol, a recent report suggests that decision-making could be normalized by lithium in patients with bipolar disorder (Adida et al., 2015). Lithium is a potent inhibitor of various phosphoinositol phosphatases, which leads to myo-inositol depletion (Huang et al., 2000; McGrath et al., 2006; O'Donnell et al., 2003). Reduced inositol levels may therefore make the link between lithium and improved decision-making among these patients. To our knowledge, no study specifically investigated the association between inositol or NAA levels and decision-making.

In the present study, we therefore used proton magnetic resonance spectroscopy (MRS) to investigate in vivo, and in humans, the relationships between levels of Glutamate, GABA, myo-inositol, and NAA, and decision-making in dorsal prefrontal cortex. We targeted the right dorsal prefrontal cortex for its known role in decision-making and cognitive control (Wallis, 2007). Moreover, we chose to use the Iowa Gambling Task (IGT) to measure decision-making. Decision-making in complex situations often necessitates learning which option is the most advantageous on the basis of trial-and-errors and experience. Although several gambling tasks are available to evaluate various decisional processes, only the IGT employs a format that integrates reinforcement learning in a relatively naturalistic fashion. For instance, while alternative tests usually require participants to make decisions on the basis of the known value of risk attributed to each possible option to choose from (e.g. in the Cambridge Gamble Task), the IGT requires the participants to acquire during the task a certain knowledge of the risk associated with each possible option to choose from. Hence, while most other gambling tasks test what is referred to as "decisions under risk", i.e., the information for making the decision are made explicit initially, the IGT also taps into what is referred to as "decisions under ambiguity", i.e., the information about the risk is initially unknown (participants are only informed that "some decks are better than others"). This process is made more complicated by the probabilistic distribution of both losses and gains creating a feeling of uncertainty. Therefore, performing advantageously on the IGT necessitates, at least initially, some implicit learning of the long-term values of each option. After several trials, the information about the risk associated with each option becomes more explicit for many participants, and IGT performance then also relies on "decision under risk". Here, we investigated the