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Agent-Centered Decision Making in Normal and Abnormal Cognition

Podell, Kenneth *[a], Funk, Brent A. [b] and Goldberg, Elkhonon [c]

[a] Methodist Hospital System, Houston, TX, USA.

[b] Henry Ford Health System, Detroit, MI, USA

[c] New York University School Of Medicine, New York, NY, USA

Avances y Desafíos en Neuropsicología

Abstract

Much of human cognition is "agent-centered," subjective, and in that sense relative, directed at deciding, "What is best for me". This is very different from "veridical" cognition, directed at finding an objectively correct solution inherent in the task and independent of the agent. The frontal lobes in particular are central to agent-centered decision making. Yet very little is available in the arsenal of cognitive paradigms used in the cognitive neuroscience research and in clinical neuropsychology test design to examine "agent-centered" decision making. Current paradigms and tests used to measure decision making clinically and experimentally are veridical in nature and as such miss the essence of "agent-centered" cognition. The dearth of "agent-centered" cognitive paradigms severely limits our ability to understand fully the function and dysfunction of the frontal lobes. The Cognitive Bias Task (CBT) is an agent-centered paradigm designed to fill this gap. CBT has been used as a cognitive activation task in fMRI, SPECT, and EEG, as well as in studies of normal development, addiction, dementia, focal lesions, and schizophrenia. This resulted in a range of findings that eluded more traditional "veridical" paradigms and are reviewed here.

Key Words:
Decision Making; Cognitive Bias Task; Cognition

Resumen

La Toma de Decisiones Centrada en el Agente en la Cognición Normal y Anormal: Gran parte de la cognición humana está "centrada en el agente", es subjetiva, y en ese sentido, está dirigida a decidir: "¿Qué es lo mejor para mí?". Esta es una perspectiva muy diferente a la de la cognición "verídica", que está más dirigida a encontrar una solución objetivamente correcta, inherente a la tarea, e independiente del agente. Los lóbulos frontales, en particular, son fundamentales para la toma de decisiones "centrada en el agente". Sin embargo, existen pocos paradigmas cognitivos en el marco de la neurociencia cognitiva y de la neuropsicología clínica, que se hayan diseñado para evaluar la toma de decisiones "centrada en el agente". Los paradigmas actuales y las pruebas utilizadas para medir la toma de decisiones clínica y experimentalmente son "verídicos" en su naturaleza y, por lo mismo, no son adecuados para la evaluación de la cognición "centrada en el agente". La escasez de paradigmas "centrados en el agente" limita severamente nuestra capacidad de entender plenamente la función y la disfunción de los lóbulos frontales. Al respecto, la Tarea de Sesgo Cognitivo (o Cognitive Bias Task, CBT) es un paradigma "centrado en el agente" diseñado para llenar este vacío. La CBT se ha utilizado como una tarea de activación cognitiva en estudios de IRMf, SPECT y EEG, así como en estudios del desarrollo normal, adicciones, demencia, lesiones focales, y esquizofrenia. Consecuentemente, se han obtenido hallazgos que evitan algunas de las limitaciones de los paradigmas más tradiciones, "verídicos", y que se revisan en este artículo.

Palabras claves:
Toma de Decisiones; Tarea Con Preferencia Cognitiva; Cognición

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1. Introduction

Neuropsychology has traditionally thrived on dichotomies in understanding brain-behavior relationships. Distinctions such as declarative knowledge and procedural knowledge or episodic and semantic memory have been used to help us better understand cognition. Here we introduce another dichotomy, which is especially critical for capturing the distinct role of the prefrontal cortex in cognition. It is the distinction between "veridical" and "agent-centered" cognition. This distinction is often ignored, or at least underemphasized in cognitive neuroscience, yet it is central to understanding the nature of decision

* Enviar correspondencia a: Ph.D. Podell, Kenneth
E-mail: Kpodell1@hfhs.org

making.

Decision making presupposes the freedom to choose, and any consideration of such freedom must eventually address the issue of its brain mechanisms. Furthermore, the examination of free choice mechanisms will benefit from employing cognitive paradigms that require choice-making in underdetermined, ambiguous environments, in which distinct rational agents may differ in their choices. Appreciation of the importance of such decision making is reflected in the philosophical literature on imprecise probability and decision under uncertainty (ambiguity) (Halpern, 2003; Keynes, 1921; Kyburg, 1974; Levi, 1974). Yet, due to tradition rather than a well reasoned research strategy, the paradigms typically deployed in cognitive neuroscience are notoriously ill-suited to address this issue. Research has traditionally relied on fully deterministic paradigms in that a subject is faced with a cognitive task characterized by a single correct response inherent to the task and independent of the agent and with all other responses being incorrect. Even in the cutting-edge applications of cognitive neuroscience aiming to model complex decision-making in environments characterized by a high degree of uncertainty (e.g., neuroeconomics, social neuroscience) the cognitive paradigms used have attached to them an “objective” metric ranking certain response selections/decisions as being intrinsically “better” than others. While free choice can be exercised in fully deterministic situations (which is reflected in the fact that rational agents often make bad decisions), the best method for fully examining the brain mechanisms of “free will,” is to use a cognitive paradigm that permits a relatively unconstrained selection among a range of choices devoid of a priori, intrinsic “quality of choice” ranking. Such a paradigm would aim to examine decision making based on subjective preference, rather than directed at uncovering the intrinsically “correct” solution. Subject preferences may be guided by both cognitive decision making as well as intrinsic somatic states (i.e., autonomic processes) that accompany the situation in which one needs to make a choice. These somatic states influence decision making and appear to be associated with ventro-medial frontal functions (Bechara, Damasio, Damasio, 2000). We call such decision making, to which a “correct-incorrect” metric does not apply, “agent-centered” (as distinct from “veridical”). By using such tasks in conjunction with functional neuroimaging, neurostimulation, and other state-of-the-art techniques one may attempt to identify the brain networks critically involved in choice selection within such unconstrained situations and thus much more realistic, situations.

Real-life cognition is dominated by “agent-centered” decision making, which ranges from trivial (choosing what shirt to wear) to life-shaping (career decisions). In either case, the “true-false” metric does not apply, since asserting that duck is an intrinsically correct choice and steak is an intrinsically false choice is an oxymoron, as is the assertion that medical school is an intrinsically correct choice and school of engineering is an intrinsically false choice. By contrast, “veridical” cognition is directed at solving problems characterized by intrinsically “true” and intrinsically “false” choices, which do not depend on the agent. Here, too, the tasks may range from trivial (5 + 5 = ?) to complex (what day of the week will be September 15, 4937?).

One can argue that in real life the cardinal decisions are agent-centered, while veridical cognition serves a supportive role, yet the arsenal of cognitive paradigms, used both in neuroscience research and as the basis for neuropsychological test design, is notoriously devoid of appropriate tools to study “agent-centered” cognition. The traditional focus on veridical cognition results in a highly contrived, artificial situation, whereby the research and clinical tools deployed to understand normal and abnormal cognition ignore some of the most fundamental aspects thereof. This lamentable circumstance particularly compromises and impoverishes our ability to understand the contribution of the prefrontal cortex to complex cognition, since the prefrontal cortex and related structures are particularly central to “agent-centered” cognition. Whereas in cognitive neuroscience research various innovative paradigms proliferate departing to various degrees from the traditional “veridical” principle in paradigm design, very little of these developments percolated into clinical neuropsychology. Even the paradigms most commonly embraced in clinical neuropsychology as the “gold standard” of the functional assessment of the frontal lobes, e.g. Wisconsin Card Sorting Test; Stroop Test, etc, (Lezak, Howieson, Loring & Hannay, 2004) are veridical in nature and thus remove the aspect of discretionary behavior as an essential component of executive functioning (Lezak et al., 2004).

More recently a distinction has been made between the "cool” and the "hot" affective aspects of executive functions (Hongwanishkul, Happaney & Lee, 2005; Zelazo & Cunningham, 2007). The "cool" (without reward/penalty) cognitive aspects of executive functions, more associated with dorsolateral regions of prefrontal cortex could be measured, for example, by WCST and Tower tests. The "hot" affective (with reward/penalty) aspects, more associated with ventral and medial regions and could be measured, for example, by Iowa Gambling Test (Bechara, Damasio & Damasio, 1994) and its variants (Kerr & Zelazo, 2004). While clearly a major step forward in the development of appropriate cognitive paradigms to assess the "frontal-lobe" functions, the currently available "hot" cognitive tasks still remain veridical rather than agent-centered, since a presumably objective "true-false" metric is commonly attached to them.

It is thus clear that very little, if anything at all, exists in the currently available repertoire of cognitive paradigms to assess "agent-centered" cognition. In order to correct this situation, a new generation of cognitive paradigms must be created, devoid of the "true-false" metric and based on subjective preference instead. In this paper we will describe such a procedure, The Cognitive Bias Test (CBT), and will review its applications to several clinical and non-clinical populations. CBT is viewed as a prototype for a whole generation of future, yet to be designed, non-veridical agent-centered paradigms.

2. Cognitive Bias Task (CBT)

The Cognitive Bias Task (CBT) is a novel, "agent-centered" paradigm that examines preferences made in a cognitive task devoid of intrinsically correct or intrinsically false choice (Goldberg & Podell, 1999; Goldberg, Podell, Harner & Riggio, 1994; Goldberg, Podell & Lovell, 1994).At the same time, it is sufficiently constrained to allow the experimenter to quantify the underlying mental processes. The CBT is intentionally simple and free of the complex plot layers which often characterize other extant paradigms used in cognitive neuroscience research in an attempt to emulate "real life," but at the cost of complicating, or even obfuscating, any possible interpretation of findings. As a result, the CBT represents an experimental cognitive paradigm that allows examination of free will, or at least "free choice," in a rudimentary and simplified form.

The CBT is designed to quantify the influence of cognitive context on response selection. It examines the subjects' response selection biases, ranging at its extremes from highly context-independent and inflexible (perseverative) to highly context-dependent (field-dependent). These two extremes are expressed as extremely low or high CBT scores, respectively. The task consists of 60 trials. Within each trial the subject is presented a simple geometric form ("target") and subsequently presented two additional geometric forms ("choices") (Fig. 1). The experimental stimuli are vertically arranged, with the target (the stand-alone shape) on top.

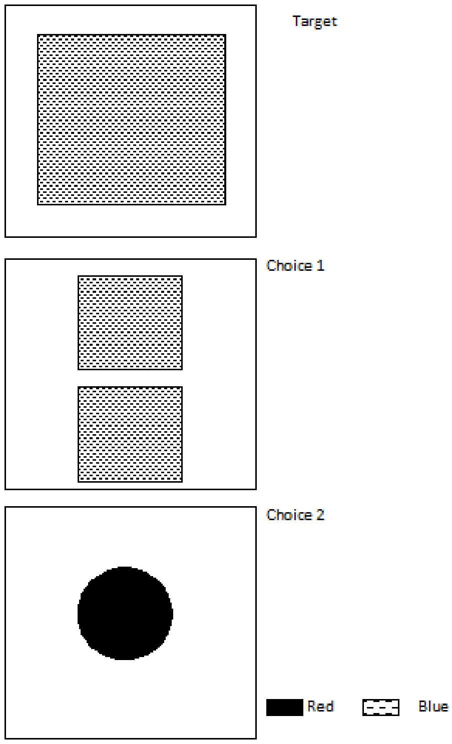

Figure 1. Sample Trial from the Cognitive Bias Task (CBT). In this example, choice #1 would yield a score of four as it matches the target stimuli along three of the five binary dimensions (color, shape, filled). Choice #2 would yield a score of zero as it does not match the target on any of the five dimensions.

The subject is instructed to look at the target and then to choose the option that the subject likes the most. The instructions clearly indicate that no choice is "better" than the other and that the subject is to indicate his or her preference. The geometric forms are characterized along five binary dimensions (shape, color, size, filled/outlined, and one/two items in the frame); thus permitting 32 different items meticulously counter-balanced in the design across trials. A number of constraints are built into the task, which are not apparent to the subject. Therefore, the individual's "free choices" are implicitly limited, and thus easily quantifiable, though the subject's impression of "free choice" remains. An example of such a constraint is that one of the choices is perceptually more similar to the target than the other. This feature of CBT permits the design of two contrasting veridical tasks that appear identical to CBT in every respect except for the instruction. Rather than asking the subject to make choices based on subjective preference, the subjects are asked to choose based on perceptual similarity or perceptual dissimilarity from the target. (For a detailed task description see Goldberg et al., 1994). The availability of two disambiguated veridical analogues is an important feature of CBT design. The "match for similarity" and "match for dissimilarity" task modifications are natural "subtraction" tasks when the CBT is used as a cognitive activation task in functional neuroimaging experiments (discussed below).

Since we designed the CBT a number of years ago, it has been used to study normal adult cognition (Goldberg et al., 1994; Stratta, Daneluzzo, Bustini, Prosperini & Rossi, 2000), cognitive development in children(Aihara, Aoyagi, Goldberg & Nakazawa, 2003), aging (Goldberg et al., 1997), cognitive characteristics of addiction (Verdejo-Garcia, Vilar-Lopez, Perez-Garcia, Podell & Goldberg, 2006), cognitive changes in schizophrenia (Stratta, Daneluzzo, Bustini, Prosperini & Rossi, 1999), and (most relevant to this project) cognitive changes following lateralized frontal lesions (Aoyagi, Aihara, Goldberg & Nakazawa, 2005; Goldberg et al., 1994; Podell, Lovell, Zimmerman & Goldberg, 1995).As noted above, the CBT has also been successfully used as an activation task in fMRI and SPECT studies (Shimoyama et al., 2004; Vogeley et al., 2003). In fact, as some authors have argued that lesion or imaging studies of healthy subjects independent of each other are unlikely to provide a completely accurate representation of how neuroanatomical structures relate to function (Rorden & Karnath, 2004). By contrast, a combination of data from both sources of evidence are likely to assist in clarifying limitations inherent in any one of them. Given that the design of the CBT is amenable to both types of studies, as demonstrated by the findings discussed here, it may serve as a particularly useful task to assist in fully understanding the functions of the prefrontal cortex. A discussion of these studies is presented in greater detail below.

2.1. Sex differences in normal subjects

Sex differences in normal cognition have long been a major theme in neuropsychological research (Springer & Deustch, 2001). As with most of the research in neuropsychology, it focused overwhelmingly veridical cognition, which has led to potentially inflammatory (and not always replicated) claims ascribing performance "superiority" on certain cognitive skills to one sex over the other. The most common among such claims is the controversial and far from clearly replicable accretion of female "superiority" in verbal cognition and male "superiority" in spatial cognition (see Springer & Deustch, 2001).

By contrast, the CBT allows one to focus on sex differences in cognitive styles rather than abilities. A wide range of individual differences in selection preferences on CBT has been demonstrated among normal, or neurologically healthy subjects (Goldberg et al, 1994; Stratta et al., 2000). Furthermore, significant group differences (e.g. sex differences) have been shown among the manner in which healthy, neurologically intact subjects exercise "free choice" (Fig. 2). Right-handed males make choices in a relatively context-dependent fashion (i.e. their choices are strongly influenced by the changing perceptual context). By contrast, right-handed females are relatively context-independent (i.e. their choices are guided by stable perceptual preferences unrelated to the changing perceptual context). Given the non-veridical nature of the CBT, these differences in response selection profiles do not reveal the quality of performance, but rather capture different response selection styles in ambiguous environments. Obviously, these findings cannot be over-generalized because of a single experimental paradigm and a limited subject sample. Our sample consisted of adults. Therefore, it is unknown whether differences reported are innate or if they arise at particular developmental stages. Furthermore, it is unknown if these sex differences in cognitive styles persist into the advanced age. Additional research is necessary to address these issues. Such findings may have interesting ramifications for the optimal didactic methods selection for females vs. males at various educational levels, for job selection counseling and vocational training, and for clinical neuropsychological assessment.

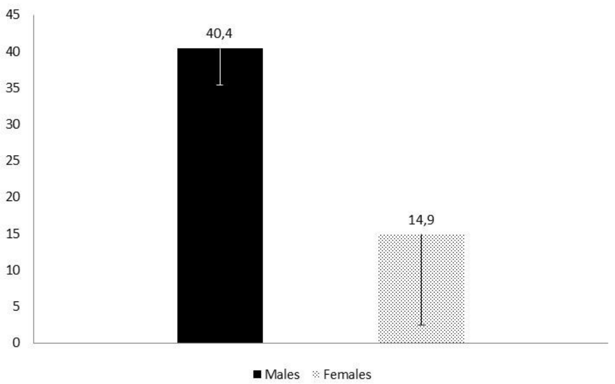

Figure 2. CBT Score by gender. A higher CBT score reflects a greater degree of context-dependent response style. A lower CBT score reflects a greater degree of context-independent response style. Error bar represents standard deviation.

2.2. Handedness differences in healthy subjects

The relationship between handedness and cognition has also been of interest for decades (see Springer & Deustch, 2001). As noted above, a considerable interaction has been demonstrated between sex, handedness, and CBT performance patterns (Goldberg et al., 1994) (Fig. 3). This finding is particularly intriguing, since most earlier attempts to demonstrate a relationship between handedness and cognitive variables have not produced robust results. It thus appears that the agent-centered paradigm instantiated in the CBT may be better suited for characterizing cognition in ways, which has eluded more traditional veridical paradigms.

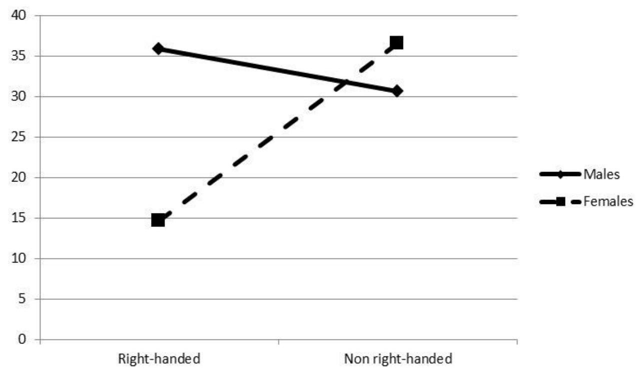

Figure 3. CBT score by gender and handedness in healthy subjects.

2.3. Functional neuroimaging studies using CBT in healthy subjects

It is tempting to assume on theoretical grounds that agent-centered decision making relies particularly on the prefrontal cortex. However, how valid is this assumption? After all, many of the executive functions measured in traditional neuropsychological research were at one point assumed to be the exclusive domain of the prefrontal cortex, an assertion that has proven false (see Lezak et al. 2004 for a review of the implication of multiple structures in executive functions). Therefore, the empirical test of this assumption is best conducted by using the CBT as a cognitive activation task in various functional neuroimaging modalities. As mentioned earlier, the CBT is particularly well suited for functional imaging research, because of its natural "subtraction" tasks. It is common in functional neuroimaging research to administer the critical task in conjunction with a baseline or other comparison tasks. The CBT has been designed in such a way that on each trial one choice is more similar to the target. This permits two "subtraction" tasks that retain all the physical characteristics of the CBT but are not preference "agent-centered" tasks: (a) match for similarity; (b) match for difference.

Patterns of regional cortical activation associated with the CBT have been studied with several functional neuroimaging modalities. Such studies have demonstrated preferential activation of the prefrontal cortex when the task was one of subjective preference-based choice using functional magnetic resonance imaging (fMRI, Vogeley et al. 2003), single photon emission computerized tomography (SPECT, Shimoyama et al., 2004), and electroencephalography (Kamiya et al., 2002).

2.4. Cognitive characteristics of addiction

What distinguishes the cognitive profile of an addict from that of healthy individuals? Likewise, are there cognitive risk factors predisposing one to addiction or cognitive consequences of long-term addiction? These questions are of great public health importance, and a large body of research exists investigating these questions. One assumption often made is that executive functions must be particularly compromised in addiction. This is a reasonable assumption, but as already noted, "executive functions" is a rather generic term that subsumes a number of loosely interrelated constructs (and neural structures), the unifying theme being that they all are somehow mediated by the frontal lobes. So how are executive functions compromised in addiction?

To address this question, Antonio Verdejo-Garcia et al. (2006) compared the performances on neuropsychological tests of heroin addicts to that of demographically matched healthy controls. The authors were particularly interested in the subjects' performances on the CBT and the Iowa Gambling Test (IGT), which is essentially veridical (i.e. characterized by intrinsically "good" and "bad" choices), but more closely mimics real-life decision making than traditional executive tasks. Indeed, the heroin addicts adopted suboptimal performance strategies on IGT. However, the CBT performance difference between the heroin addicts and healthy controls was a particularly striking outcome of the study. By contrast, there was no difference between the two groups on the disambiguated, veridical versions of CBT. These findings imply that agent-centered decision making is particularly impaired in addiction.

2.5. *Cognitive characteristics of Alzheimer's type dementia*

Efforts to characterize the cognitive impairment of Alzheimer's type dementia (DAT) have traditionally focused on memory impairment. This emphasis is also reflected in the Diagnostic and Statistical Manual (DSM-IV-TR, American Psychiatric Association, 2000) commonly used in the United States for the clinical diagnosis of mental health disorders. According to the DSM-IV, a diagnosis of any dementia specifically requires the presence of memory impairment, accompanied by an impairment in one of several other cognitive domains (the unfortunate consequences of this narrow formulation is, of course, that its mechanical application would disqualify other dementia syndromes such as fronto-temporal and Lewy body dementias). The emphasis on memory impairment in dementias has been a mixed blessing, because this focus has diverted research regarding impairments in other cognitive domains in dementias. It is now increasingly recognized that the executive functions are also extremely vulnerable in dementias.

Goldberg et al. (1997) compared CBT performance in patients with very early, or mild DAT, advanced or moderate DAT, and healthy age-matched controls. Changes in performance were evident even among those with mild DAT when compared with healthy controls. By contrast, changes in the veridical CBT version became apparent only in the more advanced or moderate DAT group. This finding suggests that the prefrontal cortex may be particularly vulnerable at even early stages of Alzheimer's type dementia; a finding that was not apparent with the use of traditional executive measures that were less sensitive to frontal-lobe function.

2.6. *Lateralization and sex differences of frontal lobe functions: lesion studies*

Hemispheric specialization has been among the central themes of neuropsychology (Springer & Deustch, 2001), but the frontal lobes have been on the periphery of this inquiry, likely because the frontal lobes were long thought of as the "silent lobes" of the brain (see Luria, 1962 for a historic review of our understanding of frontal functioning). Because the theoretical framework guiding research on hemispheric specialization has long been of verbal vs. visuo-spatial distinction, the focus has understandably been on primarily posterior cortical structures, notably on the temporal lobes (Springer & Deustch, 2001). Thus, functional lateralization in the prefrontal cortex was considered only as an afterthought. If functional lateralization in the prefrontal cortex was considered at all, it was merely as an extension of the verbal vs. visuo-spatial dichotomy: the left prefrontal cortex as the medium of verbal generativity and the right prefrontal cortex as the medium of visuo-spatial generativity (see Lezak et al., 2004).

This historic lack of interest in the functional lateralization in the prefrontal cortex is contrary to a number of morphological, cytoarchitectonic, and biochemical findings. For instance, "Yakovlevian torque" (a term coined by Robert Bilder to refer to the neuroanatomical asymmetry originally described by Paul Yakovlev) implies a wider right than left frontal pole (Lemay, 1976; Schiff, Saver, Greenberg & Freeman,1986; Toga & Thompson, 2003; Weinberger, Luchins, Morihisa & Wyatt, 1982); von Economo cell (also known as the spindle cells) are more prolific in the right than left prefrontal cortex (Allman et al., 2010); dopamine pathways are more prolific in the left than right frontal regions (Denenberg 1981; Glick, Meibach, Cox & Maayani,1979; Glick, Ross & Hough,1982; Oke, Keller, Mefford & Adams, 1978; Oke, Lewis & Adams,1980; Pearlson & Robinson, 1981; Robinson, 1979; Slopsema, Van der Gugten & De Bruin, 1982). Furthermore, some of these asymmetries are found across a wide range of mammalian species. If we are to believe there is a relationship between structure/biochemistry and function, there are two logical conclusions (a) robust functional differences must exist between the left and right frontal lobes; and (b) at least some of these functional differences are irreducible to the verbal vs. visuo-spatial dichotomy, as it would represent a uniquely human characteristic.

The reason these difference have been largely overlooked may be that commonly used veridical paradigms are not sensitive enough to, or perhaps are not altogether appropriate for eliciting, the functional lateralization in the prefrontal cortex.

Goldberg et al. (1994) studied the effects of lateralized prefrontal lesions on CBT performance and found robust hemispheric and gender differences in patients with lateralized focal frontal lesions (Table 1 and Fig. 4).

Table 1.
CBT mean (standard deviation) scores by gender and location.

	LF	LP	HC	RP	RF
Males	13 (4.2)	19.3 (5.1)	35.9 (21.8)	36.4 (26.5)	62.3 (4.2)
Females	54.4(17.8)	12 (12.0)	14.6 (12.4)	7.2 (7.2)	64.8 (2.1)

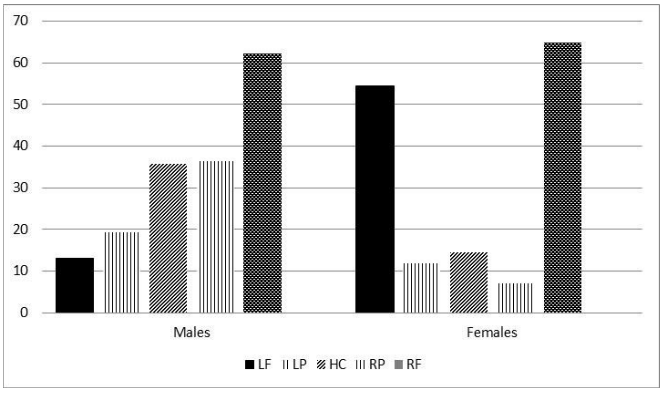

Figure 4. CBT score in right-handed male and female quadrant lesions. LF= left frontal (males=5; females=5); LP = left posterior (males=3; females=1); HC = healthy control (males=21; females=14); RP = right posterior (males=5; females=4); RF = right frontal (males=8; females=4).

In males, the lesion effects are highly asymmetric: left prefrontal lesions produced extremely context-independent (field- dependent) response selection, and right prefrontal lesions produced extremely context-dependent (perseverative) response selection relative to healthy controls. This sex difference in the degree of lateralization of frontal-lobe functions is broadly consistent with the neuroanatomical findings of a less articulated Yakovlevian torque in females than in males.

CBT appears to be more sensitive to direct frontal-lobe damage (as in stroke or neoplasms) and in more neuroanatomically specific ways, than any of the more commonly used cognitive paradigms. This becomes evident when CBT's ability to separate the effects of left vs. right prefrontal lesions is compared to that of the Wisconsin Card Sorting Test (WCST), which has been traditionally considered the "gold standard" of assessing frontal-lobe function and dysfunction (Lezak et al., 2004; Podell et al., 2004). CBT shows a clear separation of left vs. right prefrontal lesions (Fig. 5a); whereas the WCST fails to do so (Figs. 5b,c)

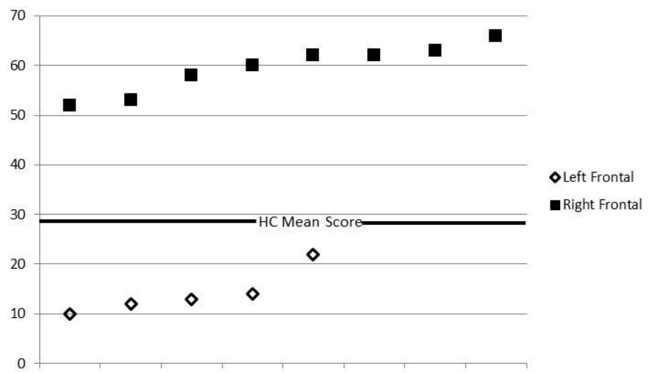

Figure 5a. Individual CBT scores in male left and right frontal lesion subjects compared to healthy control (HC) mean score.

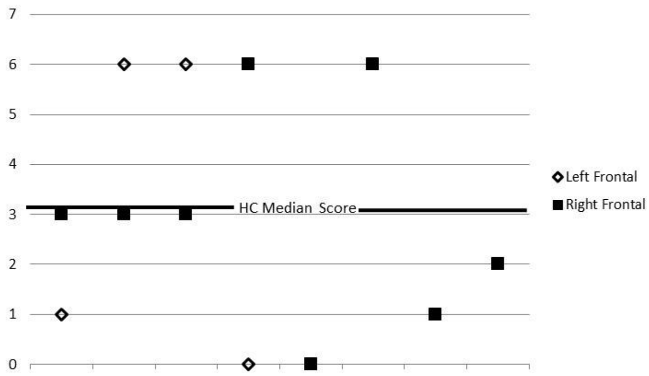

Figure 5b. Wisconsin Card Sorting Test Categories Completed in male left and right frontal lesion subjects compared to healthy control (HC) median score.

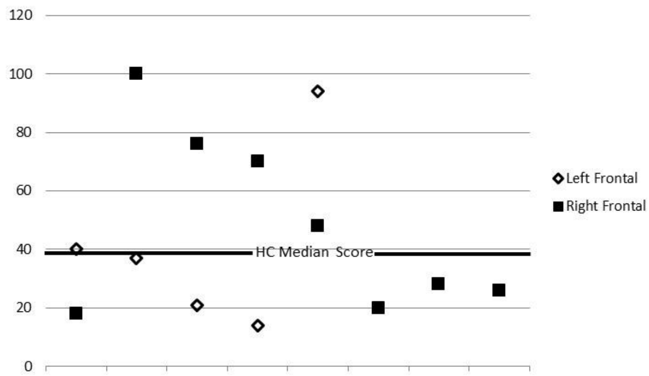

Figure 5c. Wisconsin Card Sorting Test Perseverative Responses in male left and right frontal lesion subjects compared to healthy control (HC) median score.

Another intriguing finding was obtained in a small sample of naturally left-handed patients with lateralized lesions (Goldberg et al., 1994). The effects of lesions in this cohort were distinct from, and in some way opposite to, those documented in the naturally right-handed patients (Figs 6a & 6b). While this finding is in need of replication due to very small left-handed sample size, if replicated, it may well be the first demonstration of a double-dissociation between handedness and performance on a cognitive variable.

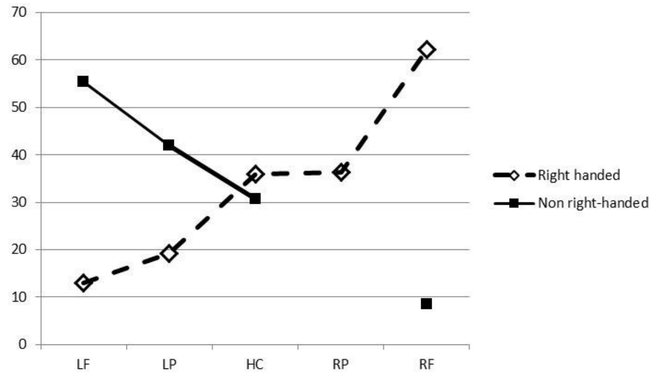

Figure 6a. CBT scores in right-handed and non-right handed males subjects. LF = left frontal (n=2); LP= left posterior (n=3); HC = healthy control (n=19); RP= right posterior (n=0); RF= right frontal (n=2).

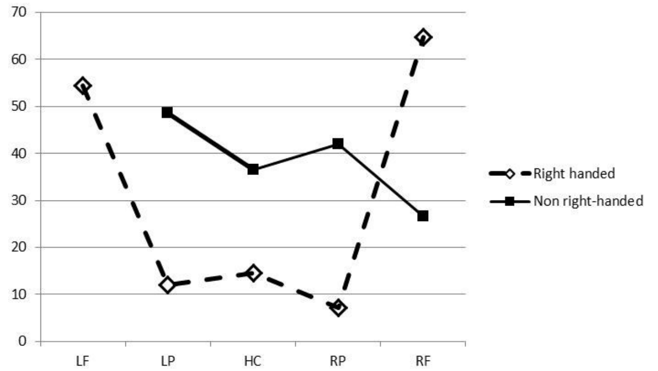

Figure 6b. CBT scores in right-handed and non-right handed females subjects. LF = left frontal (n=0); LP= left posterior (n=2); HC = healthy control (n=19); RP= right posterior (n=2); RF= right frontal (n=3).

Using the CBT in patients with lateralized frontal lesions, it was possible to show that the left and right frontal systems play different, and in males synergistically opposite, roles in response selection in ambiguous environments. These studies were among the first to examine the neural basis of choice-making in under-determined, ambiguous, "agent-centered" situations. These findings are of great potential practical importance in the design of cognitive remediation procedures individualized according to lesion side (e.g. in the anterior cerebral artery strokes), sex, and handedness in addition to the already discussed theoretical value.

Inquiry into the role of the prefrontal cortex and its different subdivisions in mediating choice-making in under-constrained environments is of great potential relevance to diverse areas, ranging from clinical neuroscience to education to neuroeconomics. Prior research, has demonstrated that the frontal lobes are central to most complex, "meta-cognitive" levels of our mental life and are particularly important in decision making in novel situations characterized by high levels of uncertainty. Although there is extensive literature on the roles of the prefrontal cortex in meta-cognition and decision making, it is conspicuously remiss in one particular regard: differential contributions of the left vs. right frontal lobes to these processes. With the contribution of the discussed CBT findings we may finally be approaching an understanding of the lateralized functional differences in the frontal lobe. However, it is still necessary for future research to determine how these lateralized differences manifest in decision making, and what the optimal integration of the left and right prefrontal contribution to decision making is.

2.7. Lateralization of frontal lobe functions: functional neuroimaging studies

Inferring the principles of normal brain functions from brain pathology has been extremely productive over the years. Nonetheless, this approach has all the pitfalls of being indirect. It is necessary to examine further the complementary hemispheric contributions to "free choice" in healthy individuals using the combination of state-of-the-art functional neuroimaging and brain stimulation with techniques such as Transcranial Magnetic Stimulation (TMS). CBT's sensitivity makes it uniquely suited to study the functional lateralization of the frontal lobes in normal subjects using functional neuroimaging, TMS and other neurophysiologic and electrophysiological techniques. Shimoyama et al. (2004) used a modified version of CBT (mCBT) as a cognitive activation task during SPECT in a sample of young adult males. Bilateral dorsolateral prefrontal activation was evident. Additionally, left inferior prefrontal activation was associated with a context-dependent response selection strategy. This is broadly consistent with the lesion studies discussed earlier.

2.8. Neurodevelopmental studies

Is the frontal-lobe functional lateralization pattern described in the previous sections fundamental, or is it an emergent consequence of something else, as observed with language acquisition? Aoyagi et al. (2005) addressed the issue by administering a modified version of CBT (mCBT) to children with left and right frontal focal lesions or epileptic foci, and to matched healthy controls. The effects of lateralized frontal lesions in children were similar to those described in adults. Thus the authors concluded that the functional lateralization properties in the frontal lobes captured by

CBT appear to be "fundamental" and "biological" in nature rather than acquired.

This does not necessarily imply that the choice behavior in underconstrained, "agent-centered" situations remains unchanged with age. There is evidence that the right cerebral hemisphere matures earlier than left, and this may affect the way decisions are made at different neurodevelopmental stages. Aihara et al. (2003) studied response selection patterns on mCBT in different male age groups. A gradual shift was evident from predominantly context-independent choice selection (5-7 years old boys) to intermediate choice selection (7-9 years old boys) to predominantly context-dependent choice selection (13-16 years old boys). This is consistent with a change in the balance of the two prefrontal systems in decision making with age.

2.9. Lateralization of frontal-lobe dysfunction in schizophrenia

Schizophrenia is being increasingly viewed as a syndrome, with many possible causes, rather than a single cohesive disorder, which makes any neuroanatomical generalization about schizophrenia potentially spurious. Nonetheless, frontal-lobe dysfunction has been reported as a relatively consistent finding across a large body of research. In particular, left prefrontal dysfunction has frequently been documented (Wolf, Hose, Frasch, Walter & Vasic, 2008). Stratta et al. (1999) administered the CBT to patients with schizophrenia and found a preponderance of context-independent reasoning in both female and male patients compared to healthy controls. This is consistent with the lesion studies described earlier in this paper, which linked extreme context-independent cognition to left prefrontal lesions.

3. Conclusions and future directions

Understanding the mechanisms of adaptive and maladaptive decision making has become one of the central themes of neuropsychology and cognitive neuroscience. Considerable strides have been made in the design of cognitive paradigms aimed at studying these processes in a more realistic context of (usually economic) gains or losses. Yet one broad domain of decision making remains largely ignored, despite its centrality to human cognition. This is the domain of agent-centered decision making, which is preference-based and to which no objective "good-bad" metric applies. In order to understand more completely the brain mechanisms of normal and abnormal decision making, we need a wide range of agent-centered cognitive paradigm. The work reviewed in this paper barely "breaks the ice" in this direction, but it is a start. Even with a single, limited paradigm represented by The Cognitive Bias Task, a number of important findings could be made, which eluded previously used veridical paradigms. These include the functional lateralization of the frontal lobes, sex differences in the functional lateralization of the frontal lobes, and others.

It is our hope that the work described in this paper will stimulate the development of an entirely new family of cognitive probes designed to assess agent-centered cognition both as cognitive neuroscience research tools and as the basis for clinical neuropsychological test design. While The Cognitive Bias Task instantiates the "agent-centered" decision making construct in a rather distilled, simple form, the future instantiation of this construct in test design may strive to be more ecologically realistic and to model a range of ecologically plausible decision-making scenarios. Another direction of future research may address the role of affective modulation in agent-centered decision making. Because of its intrinsically personal, subjective nature, agent-centered decision making is likely to be more subject to such modulation than veridical decision making. Agent-centered paradigms may prove to be particularly revealing in understanding the role of emotions in decision making in the broadest sense.

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