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Neuropsychological deficits in major depression reflect genetic/familial risk more than clinical history: A monozygotic discordant twin-pair study

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ABSTRACT

Neuropsychological deficits have been associated with major depression (MD) and persist in some individuals even after symptom remission. However, it is unclear if the deficits are a consequence of MD or are pre-existing and reflect MD vulnerability. We addressed this issue by studying 117 twins from monozygotic (MZ) pairs discordant for lifetime history of DSM-III-R defined MD and 41 twins from MZ pairs in which neither twin had experienced MD. Our assessment included a structured clinical interview and measures from the WMS-III and WAIS-III. The "unaffected" twins from discordant pairs showed the same pattern of performance as their affected cotwins on measures of attention, working memory, verbal memory, and visuo-spatial processing. Compared to twins from pairs with no MD history, twins in discordant pairs had lower performance in the domains of attention, memory, visuo-spatial processing, and general knowledge. However, after adjusting for sex and age, the groups differed only on attention and general knowledge. The similar performance of twins in pairs discordant for MD suggests that familial risk for MD has a greater influence on neuropsychological functioning than individual MD history. Findings of impairment in individuals euthymic for MD are more consistent with pre-existing deficits than scarring effects of MD.

1. Introduction

Major depression (MD) is consistently associated with attentional deficits, including selective and sustained attention, effortful processing, set-shifting and various attentional biases (Hammar et al., 2003; Lyche et al., 2010; Paelecke-Habermann et al., 2005; Weiland-Fiedler et al., 2004). MD has also been associated with other neuropsychological deficits, including impairments in memory (Hinkelmann et al., 2009) and executive functioning (Douglas and Porter, 2009), and at times verbal fluency (e.g., Gohier et al., 2009). These deficits in attention are associated with increased risk for suicidal behavior in individuals with MD (Keilp et al., 2008, 2012). Findings vary regarding the severity, duration, pattern, and persistence of the deficits after improvement or remission of active MD symptomatology (e.g., Halvorsen et al., 2012; Paelecke-Habermann et al., 2005; Weiland-Fiedler et al., 2004; Wekking et al., 2012; Xu et al., 2012). However, studies to date have not measured premorbid cognition and cannot address whether such deficits are a consequence of experiencing MD (a scarring effect) or existed prior to depression, either as a prodromal symptom or as a risk factor.

Studying identical (or monozygotic, MZ) twin pairs discordant for an outcome (e.g., MD) is a powerful method for examining the etiological relationship between the outcome and associated features (e.g., neuropsychological deficits; McGue et al., 2010). MZ pairs are matched for early family environmental and genetic factors, allowing for a clearer identification of direct mechanisms (i.e., MD causes deficits) vs. indirect mechanisms (e.g., genetic factors increase risk both for depression and deficits). In the discordant pair design, the neuropsychological performance of the twin "exposed" to MD (i.e., proband), is compared to the performance of his or her cotwin who has not experienced MD. The discordant twin design has been used to study the relation of neuropsychological deficits to the etiology of schizophrenia (e.g., Cannon et al., 2000; Goldberg et al., 1990).

Fig. 1 portrays the expected results from a MZ discordant pair design under three hypothesized models for the etiological association between MD and neuropsychological deficits. Under the

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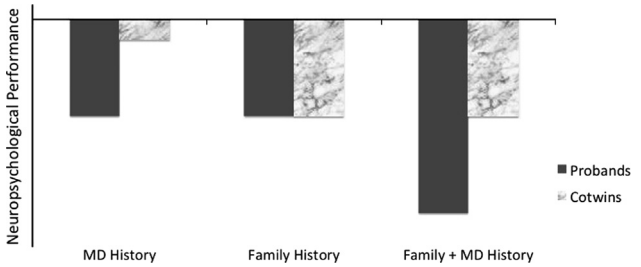

Fig. 1. Expected patterns of deficits in discordant cotwin–Control studies under alternative models for the etiological relation between MD and neuropsychological deficits. *Legend*: MD History Model: deficits are associated with clinical history of MD, probands but not unaffected cotwins show deficits relative to Controls; Family History Model: deficits are associated with family history of MD, probands and unaffected cotwins show equivalent deficits relative to Controls; Family+MD History Model: deficits are associated with both sources, as cotwins and probands show deficits arising from familial vulnerability and probands have additional deficits associated with clinical history of MD.

MD History model, neuropsychological impairments are caused by MD or other processes related to having MD. Thus, twins who have experienced MD are expected to have cognitive impairments, but their cotwins who have not experienced MD will not be impaired.

The Family History model represents the situation in which the MD-neuropsychological deficit association arises from overlapping risk factors that have a familial origin (either heritable or family environmental factors). Here, the degree of impairment (relative to a Control group) is not expected to be related to personal clinical history. In the context of discordant twin pairs, individuals without MD would show neuropsychological impairments to the same degree as their affected cotwins.

The FamHist+MDHist model combines these two scenarios; individuals with a family history of MD are expected to have neuropsychological deficits associated with this familial risk, and individuals who have had MD are predicted to have additional deficits.

In addition to studying discordant pairs, useful information comes from also studying twin pairs who have never experienced MD. Including unaffected pairs provides a comparison group for assessing the degree of deficits of the "unaffected" members of pairs discordant for MD. This Control group can serve as an anchor point for judging the impact of familial risk and MD history; the ability to distinguish between the MDHist and FamHist+MDHist models is contingent upon having a comparison group. The use of all three groups (i.e., affected probands and unaffected cotwins from MD discordant twin pairs, and healthy Control pairs) allows for the clearest interpretation of study results.

The goal of this research study was to clarify the relation between MD and neuropsychological deficits, using an MZ twin design to account for the impact of family environment and genetic risk. To our knowledge, this is the first study to apply the discordant twin pair design to examine this issue. A prior study of Danish twins (Christensen et al., 2006) evaluated the cognitive performance of 94 non-depressed cotwins of individuals with MD compared to a Control group. However, this study did not include the depressed probands for within-pair comparisons.

Our study was designed to answer three questions related to the three models portrayed in Fig. 1: first, do probands with a history of depression show neuropsychological deficits relative to their unaffected cotwins? Second, do individuals with an MD history show neuropsychological deficits relative to Controls from unaffected twin pairs? For these two questions, we also examined what clinical variables might be associated with these possible group differences. Third, assuming some differences are detected between probands and the other groups, it is of interest to know if the unaffected cotwins of probands differ from Controls.

We assessed attention, working memory, verbal memory, visuo-spatial processing and general knowledge among 158 twins from MZ pairs previously studied for personal and family history of MD. We hypothesized that attention and working memory would be consistent with the MDHist+FamHist model. That is, we predicted both probands and their unaffected MZ cotwins would perform more poorly on these measures than non-depressed Controls and that probands would perform more poorly than their unaffected cotwins on these measures due to the "scarring" influence of depression. Longitudinal study of individuals currently with, and remitted from, MD suggest that impairments in attention and frontal function are MD state-independent (Ardal and Hammar, 2011; Douglas and Porter, 2009; Hammar et al., 2003; Xu et al., 2012). Given evidence of attentional impairment from the limited literature on neuropsychological performance in families at risk for MD (Belleau et al., 2013; Christensen et al., 2006), these deficits may exist prior to MD onset. We also predicted that the differences between probands and their unaffected cotwins would be associated with the severity of proband depressive history. Depression severity has been found to impact neuropsychological performance (Austin et al., 1992; Keilp et al., 2012; Naismith et al., 2003; Paelecke-Habermann et al., 2005) though this finding is not always consistent (cf., Lampe et al., 2004; Wekking et al., 2012). Given the uncertainty in the literature regarding the association between MD and verbal memory (e.g., Austin et al., 1999; MacQueen et al., 2002; Christensen et al., 2006; Smith et al., 2006; Simons et al., 2009), we expected deficits in probands but not did hypothesize whether they would reflect the FamHist model (i.e., also present in unaffected cotwins) or the MDHist model (i.e., related to clinical history). Finally, we hypothesized that the depression-related deficits would be specific to attention and memory; while other domains of cognitive functioning have at times shown impairment in MD, attention and memory are the domains consistently impacted in individuals with MD (Hasselbalch et al., 2011; Landro et al., 2001; McClintock et al., 2010; Murrough et al., 2011; Zakzanis et al., 1998). Therefore we expected no differences among probands, MZ cotwins and Controls on measures indexing general knowledge and visuo-spatial processing.

2. Methods

2.1. Subjects

Participants are from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD), a longitudinal population-based study of genetic and environmental risk factors for psychopathology (Kendler and Prescott, 2006). The sample was originally identified through the Virginia Twin Registry,[1] and includes Caucasian twins born in Virginia between 1934 and 1974. The current sample comprises twins from two smaller sub-studies from the VATSPSUD who had neuropsychological testing. Prior to participation in this study, all subjects had been assessed with structured clinical interviews and were known to be competent. For twins in male pairs, assessments were conducted twice across a period of 2–3 years. Female pairs were assessed two to four times over a period of 8–10 years. Potential participants were mailed information letters and consent forms and then contacted to request participation. All pairs in both groups were MZ, determined by a combination of questionnaire responses and photographs, the validity of which had been previously confirmed by genotyping (Kendler and Prescott, 2006). No dizygotic pairs (DZ) were available for this study. All participants were native English speakers. Approval of this human subjects research was given by Virginia Commonwealth University's Institutional Review Board (IRB).

Eligibility for the *Discordant for Affective Disorder* (DAD) study was defined by three criteria as assessed in 2000 (Kendler and Gardner, 2001): (i) the affected member (proband) of the pair must have met criteria for one or more episodes of DSM-III-R defined lifetime MD on at least two assessments; (ii) the unaffected

[1] Now part of the Mid-Atlantic Twin Registry.