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The road not taken: life experiences in monozygotic twin pairs discordant for major depression

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Abstract

In an effort to understand how environmental experiences contribute to risk for major depression (MD), we conducted joint autobiographical interviews with 14 pairs of monozygotic twins (mean age 51.2) rigorously discordant for a lifetime history of MD. Twelve of the pairs could be sorted into four broad categories. In two pairs, discordance was associated with a single traumatic event occurring to the affected twin. In seven pairs, the well twin had one stable, long-term, successful romantic relationship, whereas the affected co-twin had romantic reversals one or more of which precipitated depressive episodes. These pairs varied in the degree to which the romantic problems seemed to arise from bad luck or poor choices. In one pair, occupational difficulties were strongly related to discordance in experiences with MD. In two pairs, several mechanisms seemed to be at work. Discordance in the quality of intimate love relationships was the most common etiological factor revealed by interview in these discordant pairs, with single dramatic events and occupational problems being considerably rarer. Even in this best of natural experiments, the causal interrelationship between personality, environment and depressive episodes was not always clear. Many pairs illustrated the protective effects of planfulness and the malignant effect of cumulative continuity where early difficulties in relationships shaped the subsequent life course. These results speak both to the importance of environmental influences on human well-being and psychopathology, and the complexity of the causal paths underlying their effects.

Keywords

adult development; environment; major depression; twins

We can therefore say that in approaching reality the empirical sciences search for either of two things: the general, in the form of natural laws, or the special, as a specific event of history. They thus contemplate the permanent and immutable, or the transitory as contained into real-life happenings. The former sciences concern laws, the latter events; the former teach what has always been, the latter what has happened once. In the first case, scientific thinking is—if we were allowed to coin new technical terms—*nomothetic*; in the second case—*idiographic* Wilhelm Windelband 1894.¹

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

‘... the distinguishing feature of causal explanations ... is that they are explanations that furnish information that is potentially relevant to manipulation and control: they tell us how, if we were able to change the value of one or more variables, we could change of the value of other variables.’ James Woodward 2003.²

INTRODUCTION AND METHODS

Major depression (MD) is a common psychiatric disorder of complex etiology. Although genetic factors have an important role in its pathogenesis,^{3,4} a number of environmental risk factors for MD have also been implicated (e.g., Brown *et al.*, Parker, Paykel⁵⁻⁷). Our best estimate of the heritability of MD is around 40%, suggesting that environmental experiences make a major contribution to risk.^{3,4}

However, although the identification of environmental causes of MD may seem straightforward, it is not. Most of the potential ‘environmental’ risk factors for MD such as traumatic life events, being poorly parented and having low social support are themselves influenced by genetic factors.⁸ Indeed, we know that genetic risk for MD is partly mediated through an increased risk for lifetime traumas, lowered social support and stressful life events.^{9,10} However, even when correcting for genetic influences, these environmental factors are still pathogenic.^{11,12} How can we disentangle environmental risk factors for MD from those associated with disease risk through shared genetic risk factors?

The study of monozygotic (MZ) twins reared together who are discordant for lifetime MD is one potential method. Because MZ twins begin life with identical genotypes and are raised together in the same family, all differences that arise between them must result either from random developmental processes or meaningful differences in environmental experiences.

In our large scale Virginia Twin Study of Psychiatric and Substance Use Disorders,¹³ we interviewed both members of > 1500 MZ twin pairs, most of them multiple times. Of these twin pairs, a moderate number were rigorously discordant for a lifetime history of MD. We have previously examined some of these pairs by applying statistical models to data collected from structured psychiatric interviews.¹⁴

This report describes results of a new project with a subset of these twin pairs. Instead of utilizing standardized interviews performed with twins one at a time, we interviewed the pair together, asking them to provide a joint autobiography. It was our hope that by having the twin pairs explain to us the origin of their life course differences, and it would help us to understand the environmental sources of their discordance for MD.

These interviews, all audiotaped, were completed with 14 twin pairs. KSK led the interview and was initially blind to which of the twins had a history of MD. LJH, who was not blind to the prior assessments, assisted. The interviews typically lasted 90–150 min. We prompted the twins to tell their own life stories, focusing on both their similarities and differences. Once the discordance in their psychiatric histories was revealed, we then asked them for their own understanding of the source of these differences. As defined by our introductory quote, this research is, by its nature, idiographic. It produced, in essence, 14 stories.

Pairs were eligible if: (i) the affected member reported one or more lifetime episodes of MD as defined by DSM-III-R criteria¹⁵ on at least two assessments, (ii) the unaffected member denied a lifetime history of episodes of MD on all assessments and (iii) the age of the unaffected twin at last interview was at least 10 years older than the age at onset of MD in her twin. Monozygosity was confirmed by DNA testing. Although this project was judged not to constitute research by the Institutional Review Board of Virginia Commonwealth University, we obtained signed consent for all twins. Although the essence of their story is

not altered, the information presented here is disguised in protect confidentiality. The age of the pairs at the time of interview ranged from 42 to 65 with a mean (s.d.) of 51.2 (7.2).

A total of 40 twin pairs were potentially eligible. We interviewed all twins who were willing to cooperate, giving preference to those living within a 2-h drive of Richmond, VA. Compared with the pairs we could not interview, those who were interviewed did not differ on sex ($\chi^2 = 0.37$, degrees of freedom (df) = 1 $P = 0.54$), age ($t = 1.18$, df = 78, $P = 0.24$) or parental history of MD ($\chi^2 = 0.46$, df = 1 $P = 0.50$). The affected member of the interviewed pairs did not differ from the affected members of the uninterviewed discordant pairs in education ($\chi^2 = 0.61$, df = 1, $P = 0.44$), number of reported depressive episodes ($\chi^2 = 0.67$, df = 1 $P = 0.41$) or number of symptomatic criteria reported for the lifetime worst episode ($\chi^2 = 0.01$, df = 1 $P = 0.93$).

RESULTS

We have organized their stories into five groups, which we now present. Because of space constraints, we provide only a brief synopsis of the life story of each pair. Table 1 lists the symptoms reported during the worst MD episode and other clinical features of the depression in the affected member of each pair. As a group, the affected twins were relatively severely ill, endorsing an average of 7.8 out of 9 'A' criteria.

The single dramatic event

In this pattern, observed in only two pairs, the development of MD in one twin, but not the other, was best understood as arising from a single dramatic event that occurred to the affected twin.

Pair 1

These 46-year-old twin brothers were easy to tell apart: David was heavier, sported a crew cut and was dressed business casual, whereas Daniel had longer hair, wore workman's clothes and had a moderately disconjugate gaze. Behaviorally, David was concise and focused whereas Daniel was rambling and digressive, with an awkward demeanor. They reported being quite similar as children; the only difference in temperament mentioned was that Daniel was somewhat more aggressive and David less assertive. The twins were raised in town but spent much time on their grandfather's farm, where at the age of 12 Daniel suffered a severe accident. He was driving a small motorcycle at a fast speed in a field when he hit a large rock, flew off the bike, landed hard and lay in the field for some time before being discovered. Daniel was in a coma for over a week, experienced high temperatures and needed several bore holes in his skull to relieve the pressure. He missed half the school year while in rehabilitation where he had to 'learn how to do everything again'. Both twins reported that Daniel's cognitive functioning was diminished after the accident; previously, he was an Honor Roll student who had both more 'book smarts' and ambition than David. After his recovery, Daniel's life continued much the same for many years—people accepted him, he retained his friends and although he was no longer 'college material', he felt satisfied. However, as an adult—with the responsibilities of a family, home and finances—Daniel was laid off from his construction job at age 28, shortly after his first son was born. He took this very hard, feeling a failure as a husband and father, and he described a lengthy depressive episode. Whereas David had a long-term steady employment, Daniel went on to experience multiple job changes and losses, resulting in additional episodes of MD. David said, "I listened to our parents more, got a decent job with retirement." Daniel described a delayed and long-term sense of inadequacy as a result of the accident, saying that even now, "I can't come to grips with the effect the motorcycle accident had on my mind." Although the accident-related changes were the distal cause, Daniel's significant struggles with

depression started much later, when, in adulthood, confronted with difficulties in his occupational life, he realized his brain injury significantly interfered with his ability to be a reliable breadwinner and, thus, a good enough husband and father. Both brothers had neuropsychological testing in another one of our studies, and Daniel had more problems than David in nearly all areas. When we inquired of the twins whether they, themselves, thought that the differences between their life courses would have been very different if Daniel had never had the head injury, both of them, especially David, endorsed this idea strongly. David said that this was the main life-changing event that impacted on his brother's psychiatric difficulties.

Pair 2

Lisa and Leslie, interviewed at age 53, were identical twins who grew up thinking they were fraternal (until our DNA testing proved otherwise). They were together constantly as children, but described their personalities as somewhat different from the start. Lisa described herself as more detail-oriented—as evidenced in the rich memories she shared with us. This strongly contrasted to her twin's frequent response of, "I don't remember." Lisa described herself as getting quickly upset over adversity, but then rapidly changing gears and focusing on problem-solving. Leslie indicated that she had more of a temper and was more assertive, more likely to 'mouth off' and get into trouble than her twin. As adults, there were notable differences in their life courses. Lisa knew she wanted to be a school teacher, attended a teacher's college and has taught for her entire career. Leslie was less certain of her career goals and held a number of different jobs, with some job changes owing to layoffs and others her choice. Lisa, at age 24, met her husband of nearly 30 years and had a big, traditional wedding. Leslie married the guy she dated in high school and college, invited only their parents to the wedding and divorced after 5 years, commenting "I picked the wrong man." As for other significant stressful life events, Lisa reported that her husband had a life-threatening illness last year, which was clearly quite stressful. However, she did not get depressed in response—instead, she went on the internet, learned everything she could about the illness and focused on 'how do we tackle this'. Late in the interview, Leslie reported (only after being asked about the most difficult time in her life) that just over 30 years ago, after drinking a modest amount of alcohol, she became pathologically intoxicated and drove onto a major highway off ramp going the wrong way. She got into the highway going against traffic and had a head-on collision, which killed the other driver—a woman with young children. Leslie was not seriously injured. Recounting this event was clearly difficult for her as she openly wept in telling us this story even after all these years. In recounting her psychological reaction to the accident, she said, "Am I really to blame for this, and then I'll have to live with this for the rest of my life? knowing there was somebody else whose family had been destroyed there." The depression following this episode was her most severe and she talked about her deep sense of guilt. Although manslaughter charges against her were dropped, there was evidence that Leslie was at fault. It was clear that with respect to their divergent histories of depression, Leslie's car accident was the defining difference between them. When we asked Lisa how she might have reacted had the accident occurred to her, she said she thought she would have gotten similarly depressed and that anybody would have. Leslie summed things up when she stated: "I've had a few things that have happened. I'm glad she (Lisa) has had everything work out for her. But, you know, it's the luck of the draw. Somethings happen and there's nothing you can do. Wrong place at the wrong time."

In pair 1, a significant neurological injury substantially impaired one twin, producing both a subjective and objective decline in cognitive functioning. However, 16 years later—when trying to retrain for a new job—his depression developed in the context of his perception of his impairments. In pair 2, the event, causing the death of another individual in a traffic

accident, produced what this twin described as a crushing psychological burden of guilt that resulted in a 5-month depressive episode. However, pair 2 did note longstanding personality differences that preceded the motor vehicle accident. We could not help wondering if her twin would have gone drinking in the bar in the first place, an event without which the accident may never have occurred.

ROMANTIC RELATIONSHIP PROBLEMS: BAD LUCK OR BAD CHOICES?

In this group of seven twin pairs—by far the largest in our study—the member without a history of MD experienced a single long-term loving and intimate relationship, whereas the co-twin had one major romantic break-up and, typically, subsequent ones, with the depressive episodes arising in the settings of these relationship losses. These twin pairs tended to self-attribute the differences in their psychiatric histories to the differences in their histories of romantic relationships, focusing on their bad luck in choice of partners. However, a more objective review suggests that for some of the pairs, the differences in the romantic history of the twin pairs could largely be understood as resulting from chance factors, whereas in others (especially the last two) these differences seem to arise to a substantial degree out of preceding temperamental differences in the twins; that is, in the latter pairs, their choices in romantic partners and the subsequent difficulties that arose appeared to be, at least in part, a result of their personalities and choices rather than largely ‘bad luck’.

Pair 3

Mike and Mitch are 49-year-old twin brothers who live down the street from one another in the countryside. They grew up with a large extended family around them, the kind that gathered at their grandparents’ house every Sunday for dinner. As the oldest two of six sons, they described themselves as ‘country boys who weren’t scared of anything’. They were inseparable throughout childhood and adolescence, and described themselves as similar temperamentally while growing up. However, Mitch was described as being rather more quick-tempered, outspoken and competitive, whereas Mike was somewhat shyer and more subdued. Together they experienced one significant trauma before adulthood, which was when their best friend was killed after he lost control of the car he was driving. Mike and Mitch were both in the car; neither twin was hurt badly and both reacted with normal grief. The twins attended community college and learned trades at which they have worked since. Mitch started dating before Mike, but both twins married at the age of 24. The major difference in their life course began when Mitch’s first marriage ended in divorce after 5 years. His wife was pregnant when they married. Mitch added that he was eager to get married and probably would have married anybody at the time. Still, he was blindsided when his wife announced she wanted a separation; he said “my whole world fell apart” and he suffered a serious episode of MD in response. Mitch learned that his wife had gotten happy feet and, after his depression gave way to anger, he decided, successfully, to fight for custody of their two young children. He reported a second episode of MD that occurred some years later, following a breakup with a younger girlfriend who was not sufficiently attentive to his children. Mitch has since remarried and spoke positively about his second wife of 12 years. Mike, in contrast, has been married to the same woman his entire adult life and reported no history of MD. Mitch joked that Mike married a much younger woman whom his twin could raise the way he wanted. When Mike was asked whether he thought he had a better sense of women than Mitch did, Mike said “I just got lucky”, and added that he thinks he would have reacted emotionally in a pretty daggone close way if he had married a woman like Mitch’s first wife. Although Mitch lamented that “the worst hurts I’ve had are from relationships with women,” he also revealed some significant problems he had had with his children, again, something his twin had not experienced. Mike talked about how

lucky he was that nothing bad had ever happened to him with his deepest relationships, those with his wife and children.

Pair 4

Cathy and Carol, 60-year-old twins, had an amusing banter throughout our interview, often disagreeing good-naturedly about their memories and observations. They readily agreed, however, that the most significant childhood event for them was their parent's divorce. Their father was away in the service much of the time during their early childhood and then left the family for good, remarrying when they were in the second grade. They grew up living with their mother and maternal grandmother, a childhood surrounded by a large extended family. Nevertheless, the absence of their father was keenly felt and he was idealized by the twins; as Cathy put it, "The absent parent is always the hero." They spoke favorably of their holiday and summer visits with their father and his new family (which included a stepsister of their age), enjoying the higher socioeconomic status (allowing them to eat out and go to shows, which they never did with their mother) and the feeling of being part of a normal family. Although both the girls were shy, well-behaved children, Carol insisted that Cathy, the first-born, was the leader and the dominant one, whereas Cathy protested this description. Nevertheless, they both gave examples consistent with it, including that they went to the same college because Cathy applied for both of them and Carol "never really made any decisions ... I just followed you." The same held true for choosing a major, with Cathy selecting business in order to develop practical skills and Carol following her even though she preferred history. Interestingly, Carol noted that she was the more rebellious of the two. A major difference that emerged was their romantic history starting in high school. Carol began to date seriously in tenth grade whereas Cathy did not have any serious relationships in high school or even in college. In college, Carol met a man 9 years her senior, widowed with two young children. They married immediately after Carol graduated. Four years and one child later the marriage traumatically fell apart; a shock to Carol. She had a severe depressive episode as a result. Much instability—in finances, jobs and housing—followed and she never remarried or even had another serious relationship, saying "divorce affects you for the rest of your life." Carol admitted to having other episodes of depression as well, starting in high school following the breakup of her first serious relationship, and later episodes related to becoming an empty nester and social isolation. In contrast to her sister, Cathy did not marry right after college, despite being pursued by a young man with an engagement ring. (Carol commented that if it were her, she wouldn't have been able to resist and would have accepted the ring.) Cathy met her future husband at age 28 and has had a great relationship with him for 32 years now. In reviewing differences in their life courses, the major one clearly had to do with their relationships with men. Cathy did not succumb to the social pressure to marry soon after college graduation, whereas Carol did. In a telling moment, Carol said something to the effect of, "I think a lot stems from the fact that I was always looking for my father." We had the sense that Carol, the younger sister, the follower, more passive and less planful, was somewhat needier, perhaps a bit more affected by the loss of their father, more eager to replace him early on—and failed in her search, which led to additional upheaval in her life. It would appear that with this pair, it is the loss of important men—involving romantic as well as familial losses—that was largely responsible for their discordance in their experiences of depression.

Pair 5

Susan and Sandra, though DNA testing confirmed they are MZ twins, look strikingly different—Susan quite a bit slimmer and a couple of inches shorter, with long, straight brown hair and glasses; Sandra with short, curly blond hair, larger and heavier than her twin. The oldest of six siblings, they described moderate temperamental differences going back to early childhood. Although both were good girls, Sandra was rather more assertive, self-

confident and the protector of her twin sister. Susan was less physically coordinated and more reserved, nervous and sickly, primarily with multiple allergies and a nervous stomach. In childhood and adolescence, one probably would have guessed that Susan was the more vulnerable twin, and therefore more likely to have later emotional problems—but that is not how things turned out. Susan dated little until at age 21 she met an older man at work; they took it slowly, not marrying until she was 29. Their nearly 20-year marriage has been quite good and without major strain; they had no children together, but she has stepchildren nearly her age with whom she is close. In contrast, Sandra got married right out of high school to a young man she started dating at 16, they had a child a few years later and their marriage ended when their daughter was 2-year-old. Sandra said they were “way too young and didn’t have any idea of what marriage was about.” She was devastated when he left—he was having an affair—and experienced a lengthy and severe depressive episode in response. The day Sandra’s husband left her, she spent the night at her twin’s house and Susan got to be the protective twin for a change. Less than a year later Sandra married a very different kind of man—focused, ambitious and considerate. However, her daughter from her first marriage had a very difficult childhood and adolescence, marked by drug abuse, court appearances and dropping out of college twice. She said her daughter has had lots of issues all through her life, getting with the wrong things and the wrong people. Sandra always felt guilty about her daughter’s problems and has spent a lot of time and money trying to help her. There has been a great deal of tension over the years between her daughter and her husband, who have barely spoken for 2 years now, and, in turn, some marital tension with Sandra’s feeling caught in the middle. She described having additional depressive episodes related to her daughter’s problems and the ongoing strain between her husband and her daughter. To sum up, Sandra—probably as a result of the problems with her first marriage, the subsequent issues with her child from that marriage and the conflicts between this daughter and her second husband—has struggled with depression, whereas her sister Susan has not. When asked whether they thought this difference in outcome was mostly ‘bad luck’ or a result of their different personalities (which led Sandra to move more quickly into a marriage for which she wasn’t suited) they thought it was some of both. Susan did describe herself as more hesitant with men, ‘going slower’ and being what might be described as more ‘risk averse’. But both seemed convinced that if Susan had been dealt the hand that Sandra was, she likely would have had as bad or an even worse an emotional reaction.

Pair 6

Donna and Debra, 51-year-old twins, were interviewed in a Sunday school classroom at the latter twin’s church. Debra came across as rather more self-possessed, calmer and self-confident, whereas Donna had a slightly more strained demeanor and looked as if she had aged somewhat more than her twin. When asked about their early years, they said they were an ‘accident’ as their parents already had three teenage children; in addition, their mother did not know she was having twins until they were born. The twins said they were blessed with a very close family. They described themselves as very similar through childhood and middle adolescence, rather easygoing, extraverted and good students. Debra, who earlier had indicated she was born first, said, “I was first at everything ... except getting married.” When they were 15, Debra met a cute guy at the bowling alley, the main social activity in the rural area where they grew up. Because their parents only allowed double-dating at that age, the young man fixed Donna up with a friend of his so that he could go out with Debra. Although Debra and this young man dated for 2 years, the relationship ended after he went off to college—in retrospect, Debra noted, “I was smart enough to get a guy who wasn’t in a hurry.” In contrast, the guy Donna was fixed up with, 6 years her senior, was in a hurry and they married 8 months later when she was only 16. Donna told us she was ‘young and dumb’ and in ‘too much of a hurry.’ The marriage lasted 10 years (producing two daughters) and Donna attributed their marital problems to ‘his attitude,’ explaining that “he married me

young, so he could raise me the way he wanted me to be raised.” With prompting from her twin and with palpable embarrassment, Donna admitted that she had an extramarital affair, which helped her to leave her first marriage; unfortunately, her second marriage lasted only 7 years as he ‘turned out to be a prick’. She left this marriage and has been married for 10 years now to her third husband (12 years her junior). Donna reported that she and her current husband are well-suited, although they have been having difficulty lately because his slothful adult son moved in with them, has no job and has not even been looking for work. In contrast to her twin’s marital history, Debra met a young man at age 18, dated him for 5 years (neither was in a rush because of earlier painful relationship breakups), and they have been married now for 28 years. Debra said, “I have a wonderful husband, he’s very good to me” and she described a happy, relatively low-stress marriage. As for other areas of their lives, Debra has been working for the same company for 26 years, whereas Donna has had a more unstable occupational history as well as financial difficulties. Debra has been more involved in organized religion and said it has “a whole lot to do with my well-being.” Donna reported numerous episodes of MD, referring to herself as ‘a basket case at times,’ whereas her twin, in contrast, was ‘the rock’ who ‘keeps me sane.’ Debra indicated that she has had relatively few highly stressful periods compared with her co-twin. In summing up, the twins placed much emphasis on the circumstances of their marriages—Debra said “my sister did not pick well” and Donna agreed that she did not make good choices. It appears that it was Donna meeting a young man, in a hurry to meet emotional or sexual needs, wanting to get married quickly and her being caught up in the excitement of that, which seems to have been the major turning point. Debra certainly was more planful in her life but whether that was a result of innate differences or circumstance was not clear to us.

Pair 7

John and Joseph, age 51, were the most laconic twin pair we interviewed, providing little detail or elaboration in their responses, making this interview shorter and rather less informative than most. Born to an older mother and with two much-older siblings, they reported a quiet and uneventful upbringing on a dairy farm, spending most of their free time doing farm chores. One temperamental difference noted from an early age was that Joseph was less talkative, less interested in other people and more likely to keep to himself. Another difference, which Joseph related to his quieter nature, was that he was held back in the third grade, so John graduated from high school a year before his twin. Both twins worked as skilled laborers and as volunteer firemen. In his 30s, John trained to become an emergency medical technician and eventually became a fully qualified medic. Joseph did not train to become an emergency medical technician because he ‘just didn’t like dealing with people very well’. He does not have to interact with many people on his day job nor on the family farm that he still works. In terms of romantic relationships, Joseph has been married to the same woman for 25 years, his one and only serious relationship. John had a few relationships before marrying his first wife with whom he had a highly tumultuous relationship. He described episodes of MD related to this marriage and its demise. John reported a happy second marriage of 7 years now. Both twins described having had serious financial difficulties during their adult lives, one declaring bankruptcy and the other foreclosing on his home. John reported an MD episode related to the foreclosure. In summary, the more outgoing twin, John, appeared to have greater depressive reactions to life’s challenges, which in his case included more romantic instability.

Pair 8

Dennis and Douglas are 55-year-old tile setters, in business together, living near one another in a town by the water. They reported having a fairly traditional upbringing and happy childhood, playing together all the time, being ‘rough and tough little kids.’ Dennis reported an attempted but unsuccessful molestation by a neighborhood man when he was 13, but he

minimized its long-term effect, saying only that perhaps it made him more self-conscious and “probably took a hit on my self-esteem a little bit.” The twins were so physically and temperamentally similar that in high school most people could tell them apart only by the cars they drove. The major area in which the twins diverged was in romance and marriage. Douglas started dating his wife of 37 years when he was 17. He sheepishly admitted that she got pregnant while they were still in high school so they hurried up and married at 18. He added that because of her own disruptive childhood, in which her mother married and divorced several times, his wife was absolutely determined that their marriage would work despite the inauspicious beginnings. Douglas stated, “I got lucky. I found a good woman who will tolerate me,” adding “I give God the glory for her.” Douglas’s family (including three children and five grandchildren) and his religion are the center of his world. In contrast, Dennis reported a series of intimate relationships ending in breakups, typically initiated by the woman. He had a couple of such relationships before marrying a woman he met at a nightclub at age 27. They divorced after he discovered she was having an affair with a male stripper. Dennis rebounded to another woman, 10 years his junior, who became his second wife. This marriage, like his first, lasted just a few years. He had several other serious relationships after that, including one with an alcoholic and another with a woman who had just left her husband. Dennis reported two episodes of MD, both following romantic reversals, noting that the breakups hit him hard because he “always thought it was going to last forever.’ Douglas added with a touch of criticism in his voice, ‘Why don’t you just summarize it by saying you made bad choices?’ He said his twin picked women who were too young and immature: “A pretty young lady comes up to you and puts a little glister in your eye and all reason goes out the window!” Dennis agreed that he was ‘always a sucker for that,’ after which his twin added more sympathetically, “Dennis could never really find the right woman that was willing to hang around and make a life with him. He’s had some rough luck when it comes to women.” Dennis perhaps summed it up with this statement: ‘It goes to show, I don’t care if we are identical twins, we all are individuals, and we both are programmed differently.’ It would appear that his relationship difficulties—which led to problems with depression—may reflect a lack of planful competence in making choices when it comes to selecting a partner.

Pair 9

Julie and Joyce, 44-year-old twins, both have bubbly personalities and an obviously quite close, affectionate relationship. Early on their parents nicknamed Joyce big J and Julie li’l J to reflect differences in size (Joyce was born bigger and remained so) as well as temperament. From early, on Joyce was the leader and ‘boss’ and Julie the follower. They agreed that their mother had a clear preference for, babied and made excuses for Julie, while having much higher expectations and being much more demanding of Joyce. Although the twins were always the best of friends, sharing interests and doing ‘everything’ together, temperamental differences were prominent from an early age. Joyce was more conventional and controlled, more the rule-follower and more academically motivated (she completed college and went on to be a nurse). Julie was more anxious and easily upset, less motivated about school (she dropped out of college), more impulsive and thrill-seeking and less planful. She was ‘wilder’ as a teenager, drinking more and earlier, and dating earlier and the kind of boys ‘you don’t bring home.’ At the age of 18, Julie had a whirlwind courtship with a handsome rodeo rider whom she married at 19. He was verbally abusive and had multiple affairs, yet she stayed with him for 11 years, fearing she wouldn’t have money or be able on her own to take care of herself and her three children. After she finally ended her marriage, she went on to have a tumultuous 6-year relationship until she came home and found this man in bed with another woman. Then she had a series of relationships with younger men, none of which turned out positively. Julie reported multiple episodes of significant depression, the worst related to her marriage and all related to romantic relationships. When

Joyce talked about her twin's capacity for making 'bad choices' when it came to men, Julie admitted that she has been 'depressed all the time over some guy.' In stark contrast, Joyce has been married for 23 years to a banker, a man she described as a steady, loving husband and wonderful father. He was, she said, a bit boring at first, but has grown on her over the years. For this pair, it did not seem like their choices of men were by any means accidental. In fact, Joyce said she had had boyfriends who were 'more fun,' more exciting than the man who became her husband, but she knew he was 'the kind you marry.' Julie admitted she had a sense that the man she married was a poor choice but agreed to marry him after having a 'fit of jealousy' seeing him dance with another woman. These twins had pronounced and consistent temperamental differences starting back in early childhood (as well as starkly different relationships with, and expectations from, their mother) which shaped their experiences in the early adult transition and beyond. Julie was more rebellious, more concerned with having a good time and less planful about the possible consequences of her behavior. Joyce by contrast was more conventional, more dependable and particularly planful. The difference in their history of depression seems to relate directly to Julie's repeated romantic reversals, which resulted from her poor choices in romantic partners.

Occupational difficulties

In this one pair, differences in occupational stability versus instability and the associated economic difficulties had a major role in their lifetime discordance for MD.

Pair 10

Robert and Richard, 44-year-old male twins, looked quite alike, even having matching haircuts and facial hair. The men were obviously as emotionally close as physically similar. Both men were good historians, with Robert noticeably more talkative during our interview. Their childhood was marked by instability, with repeated moves as their father changed jobs and then their parents divorced. The boys were best of friends but described some temperamental differences starting in childhood. Robert reported some childhood fears, somatic symptoms following his parents' divorce and what sounded like a general predisposition toward anxiety relative to his twin. Richard had a somewhat easier, less demanding temperament and was dubbed the peacemaker by their mother. Although both were A/B students, Robert was a bit less academically inclined and more dyslexic. Both were very active in sports and when they went off to the same college, Robert played on the football team. He had the more difficult transition to college, reporting significant emotional upset at that time and attributing it in part to his frequent football practices leaving him less time for socializing. The biggest difference the twins described was in their academic and career paths. Richard said he always knew what he wanted to do—major in library science and work in the public library system. Richard did just this, rising through the ranks to a head administrative position in his city's library system with stable employment in his entire adult life. In contrast, Robert ended up majoring in business without a clear career goal in mind. He described something on the order of ten different jobs, sometimes changing jobs of his own accord, other times being fired, laid off or suffering a business failure. He started several businesses that ended up folding. Some of these financial losses seemed to be due to bad planning or lack of due diligence, but he felt they were all because of unforeseeable circumstances. Job problems in turn caused financial problems and even bankruptcy at one point; he said money is his biggest frustration and also the primary source of stress in his marriage. Robert reported episodes of depression related to these job and financial stressors, whereas Richard has not experienced any MD. Interestingly, when asked about the twins' different outcomes, Robert thought it was attributable mostly to 'bad luck' with a little due to his being more risk-taking and ambitious than his twin. In contrast, Richard thought their different outcomes were mostly because of their different approaches to life, especially his greater planfulness relative to his twin, with only a bit due to 'luck of the draw.' We're

inclined to think the truth lies somewhere in between: that there were temperamental differences between them that contributed to Robert's adversity with his jobs, which in turn led to financial difficulties, which in turn caused family pressure, a combination of 'inside' things and bad luck that led to his episodes of depression.

MIXED CAUSES

We end with two pairs who present a mixture of the themes that were more clearly displayed in the histories outlined above.

Pair 11

Mary and Margaret, 63-year-old twins, share a house with Mary's husband and their elderly parents. Only children, the twins have had an exceptionally close relationship their entire lives, yet they described early and lasting temperamental differences. Mary was always interested in stereotypically feminine, maternal pursuits—baby dolls early on, then makeup, clothing, accessories, babysitting and boys—whereas Margaret was a classic tomboy, very sports-oriented and with little interest in the aforementioned things. Mary was the twin who was the more social and extroverted of the two, always taking care to include Margaret in her social activities. When not talking to friends on the telephone, Mary might be out shopping with her mother or assisting her in the kitchen; in contrast, Margaret was likely to be outside playing sports with the neighborhood boys or tossing a ball with her father. The twins went off to college together, chose the same major (physical therapy) and went on to long and successful careers, with Margaret choosing a more academic route and Mary a more clinical career. In terms of romantic relationships, again the contrast was evident. Although Margaret did have a serious relationship in which she was engaged to be married, she chose to end it, having decided that marriage and children were not her goals (she mentioned that she hasn't dated since her 30s). She denied depression following the breakup or at any other times in her life. Mary, in contrast, reported episodes of MD linked to romantic rejections; in each case she had hoped to get married and have a family. Another depressive episode followed an abortion about which she was very conflicted; she had quite an emotionally difficult period after this, given her strong desire to be a mother. Mary eventually married at age 51 and has derived great satisfaction from her marriage and step-grandchildren. In terms of their outcomes, two factors stand out with this pair. First is environmental discordance: objectively, Mary had substantial romantic reversals she did not initiate as well as an abortion, all life events that her twin did not face. Second, Mary was much more invested from a young age in the feminine nurturing role, strongly yearning for marriage and children, and was thus quite vulnerable to the depressogenic effects of her romantic reversals and abortion. These events were so potent because they reflected her failure to achieve marriage and motherhood, two goals that were a fundamental part of her self-identity. In other words, her depressions appeared to arise out of an interrelationship between prior vulnerabilities and the nature of the particular adversity.

Pair 12

We had our first clue that this was not the closest of twin pairs when, during a scheduling phone call, Patricia said if Pamela started blaming her again she would not accept those toxins and might end the interview. Fortunately, the interview was completed (via conference call, as the twins live in different states, both at a distance from Richmond), but there was an underlying tension that we had not experienced in other interviews. Patricia came across as more self-confident, Pamela more bitter. Born to older parents with three teenage sons, Patricia said they grew up in a household with a lot of different stresses beyond our comprehension. They described their family of origin as marked by arguments, conflict and criticism. Temperamental differences were apparent early on. The twins agreed

that Patricia was more extraverted and Pamela more introverted. Pamela remembered Patricia as tending to dominate and Patricia remembered Pamela as a crybaby. Both had strong perfectionist tendencies and were high achievers in school, with the school librarian once commenting, “those girls are going to have nervous breakdowns.” But the twins agreed that Pamela was always more the worrier. When asked how they felt about being twins, Pamela said “it was horrible” and Patricia complained about the lack of privacy. They both especially disliked that everyone treated them the same, like they were a single person, rather than the two unique, different people they were. Describing themselves as ‘frenemies,’ Pamela and Patricia chose different colleges, wanting to be apart and shed their twin identity. It was during their college years that their life courses began to diverge more substantially. Patricia became less engaged in and concerned about academics, whereas Pamela became even more focused on and worried about them. Patricia met her future husband at age 20, married just out of college and described her family life in glowing terms. Although trained as a teacher, Patricia stopped working after her children were born and appeared to derive great satisfaction as a wife and mother, denying any periods of significant depression. Pamela’s adult life, in contrast, has been full of ambition, tumult, stress and psychiatric symptoms. She described with little detail a mild depressive episode in high school and then a long, severe depressive episode that began while in graduate school and extended into her period of subsequent occupational difficulties. She got an advanced degree in Divinity at a prestigious school. She spoke openly of her sense of inadequacy there, being only ‘a small town southern girl.’ She became an ordained minister, which was a very painful process marked by bias against ordaining a woman. She described a rocky career in the ministry with numerous jobs. She married but did not describe her relationship in as unconditionally warm and supportive terms compared with Patricia; her one daughter was described as especially gifted but quite challenging to raise. Pamela was diagnosed with Multiple Sclerosis in 2003, adding yet another serious challenge to her life. Patricia attributed her twin’s long history of MD largely to attitude, saying that Pamela “always wanted people to feel sorry for her,” ‘always saw herself as a victim’ and has “taken seeing things negatively to an art form.” For this pair, it appeared that Pamela and Patricia began life with relatively modest temperamental differences but these became substantially exaggerated over time. Pamela took on more challenges and her somewhat more difficult temperament made her respond more strongly to some of the difficulties in her life. Pamela both seemed to select herself into more stressful circumstances and to react more strongly to the adversity to which she was exposed.

Pair 11 was perhaps the pair with the most striking self-reported temperamental differences—even more so than pair 9. Margaret, having decided that marriage and family were not for her, had a successful and rewarding professional career and a warm relationship with her twin. Mary, by contrast, had deep yearnings for a husband and family and was repeatedly disappointed in these aims until relatively late in life.

Pair 12 stands out more starkly than pair 10 in the differences in the career paths of the pair. Pamela, deeply religious, obtained an advanced degree and fought against sexism in a traditional Christian denomination. Perhaps she challenged herself beyond her emotional limits, finding support for her career in only a limited number of places. Patricia lived a far easier and less stressful but also less ambitious life.

Remaining pairs

In the two remaining pairs, despite a lengthy interview, no coherent story emerged about the nature or causes of the MD in the affected twin. In one pair, 44-year-old females, the affected twin described what sounded like a severe endogenous depressive episode without psychosocial precipitants. In the second pair, 59-year-old male twins, depressive episodes in the affected twin may have been related to severe earlier alcoholism.

Subthreshold episodes and family history

We examined our prior structured interviews for subclinical depressive episodes. These were reported for the unaffected members of pairs 1, 4 and 9 and the clearest episodes were associated, respectively, with death of their grandmother, caring for their dying mother and financial difficulties.

What was the level of familial risk for MD in these discordant MZ pairs? We obtained parental histories of MD in all twins in our study using the Family History Research Diagnostic Criteria.¹⁶ Compared with all MZ twin pairs in our sample where neither member had a lifetime history of MD, our interviewed pairs had a much higher rate of MD in mothers (46.2 versus 20.2%, $\chi^2 = 5.18$, $df = 1$ $P = 0.02$) but a similar rate in fathers (7.7 versus 12.8%, $\chi^2 = 0.21$, $df = 1$ $P = 0.65$). Compared with all MZ pairs concordant for a lifetime history of MD, our interviewed pairs had a similar rate of MD in mothers (46.2 versus 55.4%, $\chi^2 = 0.41$, $df = 1$ $P = 0.52$) but a significantly lower rate in fathers (7.7 versus 39.5%, $\chi^2 = 5.18$, $df = 1$ $P = 0.02$).

DISCUSSION

These twin pairs constituted on the one hand an intriguing natural experiment and on the other a source for contemplation of the inherent problems of inferring causal pathways in lived human lives. No person ever gets to live life twice. If we want to ask the natural, counter-factual question about a life—that is, ‘how would it have been different if ...,’ the closest we will ever come to an answer is by studying MZ twins and co-twins reared together in the same family. By exploring, in an autobiographical manner, the differences in the life experiences of such pairs carefully picked to be discordant for their lifetime experiences of MD, we hoped to come to an understanding of the ways in which environmental experiences contribute to MD that would be difficult to achieve by other means. We had hoped that most pairs would reveal a single clear environmental cause of their discordance for MD. However, even in this best of natural experiments, the complexity of a lived human life rendered the causal pathways to MD nuanced and tentative.

We would emphasize seven features of our results. First, by far the most common explanation that emerged from our interviews with the twins about the sources of their discordance in lifetime experiences of MD related to differences in their intimate love relationships. The pattern was surprisingly similar across a number of our pairs. The well twin had a single, stable long-term marital relationship. The twin with depressive episodes, by contrast, had one early traumatic breakup of a romantic relationship that was associated with their first depressive episode, but other romantic problems often followed, which frequently precipitated other depressions. Pair 11 revealed a different pattern—one member deciding to avoid marital and romantic commitments and staying depression free. In a prior interview from a discordant pair that we were unable to interview for this project, the well twin, who was a nun, told us that she decided in late adolescence that she just could not handle men and romance, and sought a career in serving God. Her co-twin had multiple failed relationships and associated depressive episodes. These results are congruent with a large prior research literature, which has spoken of the potency of loss, in general and romantic rejection, more specifically, as a depressogenic life experience.^{5,17–19}

Second, despite the strength of the association between lifetime romantic difficulties and MD, the causal paths involved were not always clear. The interpretational dilemma was similar across a number of pairs. Was the pathway simple and clear (romantic breakup → MD) or more complex and ambiguous (personality → poor romantic choices → romantic breakup → MD)? In some pairs (for example pair 3), our sense was that the event was largely fateful—and the first simple causal path was operative. In others (pairs 8 and 9), the

more complex path seemed more likely with the twin actively selecting themselves in a romantic relationship that had a high likelihood of trouble. This realization was a humbling experience. In this ideal of situations, it was still clear that an individual's personal experiences are an entwined mix of how they construct their world and what that world does to them outside of their control.

Third, as we listened to the life stories of many of the pairs, they seemed to differ in their degree of planfulness, which other authors have found to be associated with successful adult development.^{20–22} With substantial consistency, the less planful of the pair was the one who developed MD. This was especially true in the choice of romantic partners. We see this in pair 4 where Carol rushed into her romantic relationships, whereas Cathy took her time finding a much more appropriate partner. In pair 10, Richard seemed more thoughtful and planful in his career path, whereas his twin Robert was more impulsive. In pair 9, this contrast was especially stark. It would be hard to find a more striking contrast in their husbands—Joyce with the staid banker and Julie with the handsome rodeo rider! Pair 5 displayed a similar pattern, with Sandra getting married too young and Susan taking her time, making a much more successful match. However, this pattern did not always turn out the same way. Pair 8 stands out in sharp contrast. Here Douglas was the one who married quickly (because of a premarital pregnancy), whereas Dennis took many more years to get married. But Douglas got lucky and found a wife determined to build a life-long relationship and stable marriage and family. Dennis was less fortunate in his choice of partners.

Fourth, it was rare for one major life event to cause the life course of the twins to diverge. Although relatively clear in their causal effects, these highly disruptive single fateful events are uncommon as the cause for onset of MD.

Fifth, differences in occupational stressors helped explain discordance in two pairs (clearly in 10 and somewhat less clearly in 12). In both pairs, the twin with MD had a difficult and failure-filled occupational career, whereas the co-twin either had a single fulfilling job throughout his life (pair 10) or chose to be a homemaker (pair 12).

Sixth, these stories illustrate, as pointed out by prior research,^{23–26} how moderate temperamental differences can magnify themselves across the life course. Describing a process called cumulative continuity, Kendler *et al.*²⁵ note that it

... arises when an individual's interactional style channels him or her into environments that themselves reinforce that style, thereby sustaining the behavior pattern across the life course through the progressive accumulation of its own consequences.

This sort of cumulative continuity occurs because we humans create and shape our social environment in part based on our temperament. Although this process is substantially influenced by genetic factors (e.g. Caspi *et al.*²⁶), our study shows that individual-specific environmental factors also have a role. In several of our pairs, some kind of early environmental differences produce dissimilarity in personality that in turn leads to the creation of different patterns of social, interpersonal and intimate relationships. Pair 9 clearly reflects this process. For uncertain reasons, the two twins had personality differences from a young age. As they grew and entered adulthood, their personality dissimilarities impacted dramatically on their life choices that in turn produced substantial differences in their psychiatric histories.

Seventh, our findings map with considerable congruence onto prior studies characterizing environmental influences on neuroticism (or closely related traits), a personality dimension strongly related to risk for MD.^{27–29} Successful romantic relationships and satisfying jobs

(associated with non-affection in our discordant MZ pairs) predict declining levels of neuroticism.^{30–33} Poor quality relationships, divorce and repeated bouts of unemployment (all associated with affection in our discordant pairs) are associated with increasing neuroticism levels.^{32,34,35} For individuals like the members of our twin pairs born with an intermediate level of familial risk to MD, supportive relationships and satisfying work experiences will tend to be associated with lower levels of neuroticism and a low risk for depressive episodes whereas the opposite would be predicted for relationship difficulties and/or repeated job problems.

In a time when all attention is turned to the genome with remarkable advances in techniques of genotyping and sequencing, the story of these twins speak to the basic importance of environmental influences on human well-being and psychopathology. Our results agree with a large-scale analysis of MZ twins from eight distinct samples followed longitudinally.³⁶ Differences between members of these pairs for their levels of depressive and anxious symptoms grew substantially over the human life span. Consistent with the results of our small study, these findings speak to the result of cumulative environmental experiences on our vulnerability to anxiety and depression. That is, well into adult life, our moods are not only due to genetic differences between us, but substantially shaped by our cumulative environmental experiences.

Our qualitative results are also congruent with our prior statistical study of 72 pairs of female MZ twin pairs discordant for MD.¹⁴ In that study, based on structured interviews performed separately with each twin, the lifetime stressor most closely associated with risk for MD was a history of divorce (odds ratio = 6.2). But, interestingly, our analyses also supported the continuity of stressors over time. In the year before the interview (which was typically long after the onset of MD in the affected twin), compared with their unaffected co-twin, the twin with depressive illness reported a greater number of total stressful events and higher rates of two classes of events: romantic problems and job loss.

Limitations

Our findings should be interpreted in the context of three potentially important methodological limitations. First, our efforts relied critically on the joint accuracy of recall of these twins. Amusingly, it was not uncommon for one to correct the memory of the other, for them then to briefly argue and come to a consensus about events of the past. Much more rarely, they ended up disagreeing about what actually happened. Retrospective memory errors and false causal attributions as a part of a striving after meaning are always possible and could have substantially distorted the results we obtained. Second, this research project was, in the framework of Dilthey³⁷ and Jaspers,³⁸ seeking for reasons for behavior, in this case the development of MD, using our first-person perspective honed by our empathic skills and clinical training. In Jaspers terminology, (³⁸), such reasons lead to an understanding. This is in contrast to seeking for causes—by objective third-person scientific facts established by systematic observation and statistical analysis. The association between these two kinds of knowledge about psychiatric disorders is not straight forward,³⁹ and we cannot assume that reasons for illness that we discover through speaking with our patients and understanding their stories all represent causes. However, in this case, our stories obtained from these detailed interviews were broadly congruent with statistical analysis of data obtained from prior standardized research interviews. This suggests that at least some of the reasons that emerged in our unstructured interactions are likely to also represent causes. Third, our sample size was modest and made up only of white native-born Virginia twins. We cannot be sure how well any lessons learned in these twins would extrapolate to other populations.

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TABLE 1

Clinical features of the depressive illness of the affected twin including DSM-III-R A criteria reported at their worst episode

Famno-ID	Age at interview	Depressed mood	Loss of interest	Weight or appetite change	Sleep disturbance	Psychomotor agitation or retardation	Fatigue/low energy	Guilty or worthless	Diffic. think./conc.	Suicidal ideation or attempt	Onset age	# of episodes	Longest episode	Impairment/distress ^a	Tx
1	46	x	x		x	x	x	x		x	28	3	4 years	mod/very	x
2	53	x	x	x	x		x	x	x		22	2	5 months	mod./some what	
3	49	x	x	x	x	x	x	x	x		29	2	9 weeks	mod./very	
4	60	x	x	x	x	x	x	x	x	x	26	6	6 months	Severe/very	x
5	47	x	x	x	x		x	x	x		26	3	4 months	severe/very	x
6	51	x	x	x	x	x	x	x	x		17	4	6 weeks	severe/somewhat	x
7	51	x	x	x	x	x	x	x	x		22	6	4 weeks	severe/very	
8	55	x	x	x	x	x	x	x	x		27	2	1 month	severe/somewhat	
9	44	x	x	x	x		x	x	x		22	6	3 months	mod/very	
10	44	x	x	x	x	x	x	x	x		18	3	4 months	mod/very	
11	63	x	x	x	x	x	x	x	x	x	22	3	6 weeks	severe/very	x
12	55	x	x	x	x	x	x	x	x	x	16	15	9 Years	severe/very	x

^aImpairment was assessed on a 3 point scale: none, moderate, severe; level of distress was assessed on a 4n point scale: none, somewhat, moderately and very distressed.